Outcome of patients with stage IV high-risk Wilms tumour treated according to the SIOP2001 protocol: a report of the SIOP Renal Tumour Study Group.

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Abstract

Introduction: High-risk (HR) metastatic (stage IV) Wilms Tumours (WT) have a particular poor outcome. **Methods:** Here we report the results of HR (Diffuse Anaplastic (DA)- or Blastemal Type (BT)) stage IV WT treated according to the HR arm in the SIOP2001 prospective study. **Results:** From January 2002 to August 2014, 3559 patients with WT were included in SIOP2001 trial. Among the 525 patients (15%) with metastatic WT, 74 (14%) had stage IV HR-WT. Median age at diagnosis was 5.5 years (range: 1.4-18.3). Thirty-four patients (47%) had BT-WT and 40 (53%) had DA-WT. Five-year Event-Free-Survival (EFS) rates were 44±17% and 28±15% for BT-WT and DA-WT, respectively (p=0.09). Five-year Overall Survival (OS) rates were 53±17% and 29±16% for BT-WT and DA-WT, respectively (p=0.03). Metastatic complete response after preoperative treatment was significantly associated with outcome in univariate and multivariate analyses (HR=0.3; p=0.01). Postoperative radiotherapy of metastatic sites might also be beneficial. Forty-three out of 74 patients experienced a relapse or progression predominantly in the lungs (80%). The median time to relapse/progression after diagnosis was 7.3 months (range: 1.6-33.3) and 4.9 months (range: 0.7-28.4) for BT-WT and DA-WT, respectively (p= 0.67). This is the first prospective evidence of inferior survival of stage IV BT-WT as compared to historical IR-WT. Survival of patients with stage IV DA-WT has not improved compared to the previous SIOP93-01-study. **Conclusion:** These results call for new treatment approaches for stage IV HR patients.

Introduction

The International Society of Pediatric Oncology (SIOP) strategy for Wilms Tumour (WT) is tailored to the patient based on overall tumour stage at diagnosis (localised, metastatic (stage IV), or bilateral (stage V) disease), histological risk group and local stage of the primary tumour after preoperative chemotherapy and nephrectomy (stage I-III), and response to preoperative treatment of metastatic or bilateral disease (1). With this approach, survival has risen to a current cure rate of more than 90% for patients with localized disease and intermediate- or low-risk (IR/LR) histology (2). Stage IV disease occurs in 12-20% of patients at diagnosis (3–5). The survival rates of stage IV patients reach 90% in case of IR/LR histology and metastatic complete response (m-CR) after preoperative chemotherapy and surgery. However, almost 20% of children with metastatic WT at diagnosis die (3). The negative impact of diffuse anaplasia (DA) on survival has been widely demonstrated (6–9). In patients with metastatic disease enrolled in the previous SIOP 93-01 trial, DA-WT had been associated with a lower 5-year event-free survival (EFS) compared with IR/LR histology (33.3% vs 76.8%, $p < .001$; hazard ratio, 3.6; 95% CI, 1.7 to 7.6), thus being confirmed as one of the most important prognostic factors in WT (3). The blastemal subtype (BT-WT) has been associated with poor outcome based on SIOP93-01 results (10,11) and therefore defined and treated as "high-risk" (HR) histology in the prospective international SIOP2001 study (12). A recent report showed improved survival for localised BT-WT as a consequence of intensified treatment (13). We thus analysed whether this effect can also be documented in the stage IV cohort and present the outcome of patients with stage IV HR (DA- and BT-WT) WT treated according to the SIOP2001 protocol with an intensified postoperative schedule.

Patients and methods

Patients

Patients with metastatic BT- and DA-WT were prospectively included in the SIOP2001 study from 2002 to 2014. Clinical data were retrieved from the SIOP2001 database and through national coordinators and/or local centres. Written informed consent was obtained from all the patients or from at least one parent/legal guardian. The SIOP2001 study was submitted to the European Clinical trial register (EudraCT no: 2007-004591-39). Ethical approval was obtained in all countries.

Treatment

Treatment for stage IV HR WT in SIOP 2001 is summarized in Figure 1.

Preoperative treatment consisted of a 6-week regimen (AVD) as follows: vincristine weekly (1.5 mg/m^2, max 2 mg), actinomycin D (45 micrograms/kg; max 2 mg) at week 1, 3 and 5, and doxorubicin (50 mg/m^2) at week 1 and 5 (2/3 reduction applicable to patients <12kg). A reassessment imaging of local tumour and metastatic sites was performed before tumour-nephrectomy after week 6 of preoperative treatment. Local staging and histology risk group was assessed according to the revised SIOP Classification for Renal Tumours (12).

In case of HR histology, postoperative treatment consisted of cyclophosphamide (450 mg/m^2 for three consecutive days)/doxorubicin (50 mg/m^2 one day) in postoperative week 1, 7, 19 and 31 (maximal cumulative dose of anthracyclines = 300 mg/m^2) alternating with etoposide (150 mg/m^2)/carboplatin (200 mg/m^2) for three consecutive days in postoperative week 4, 10, 13, 16, 22, 25, 28 and 34. Flank radiotherapy (RT) of 25.2 Gy (with 10 Gy boost in case of macroscopic residues or involved lymph nodes, according to physician's decision) was given to all stage III HR patients and to stage II patients only in case of DA histology. The entire peritoneal cavity was irradiated to a maximum of 21 Gy in case of intra-peritoneal dissemination.

Metastasectomy was performed after nephrectomy whenever possible in case of persisting lesions. RT of metastatic sites (m-RT) such as lungs, brain and bone was recommended regardless of the response to chemotherapy. In case of pulmonary metastases, whole lung RT was applied to both lungs, for a total dose of 15 Gy with fractions of 1.5 Gy and a boost of 5-10 Gy on any residual disease after surgery. In case of extra-pulmonary metastases, RT was applied respecting the adjacent organs.

Statistical analysis

EFS and OS at 5 years after diagnosis were estimated by actuarial methods of Kaplan and Meier, and comparisons were made with the log-rank test. Univariate survival analysis was performed for metastatic burden (<1 site versus ≥ 2 sites), metastatic response after preoperative chemotherapy, stage of the local tumour and histology. A multivariable model was constructed including all variables that were tested univariately with a $p<0.2$, and based on the Cox proportional hazards model. Continuous variables were described as mean value ± SD if the distribution was normal ($P>0.05$, Kolmogorov-Smirnov), or as median and range value if the distribution was not normal. Comparisons by histology were made using the parametric and non-parametric test whenever appropriate. We used IBM SPSS Statistics 25.0.

Results

Patients' characteristics

From January 2002 to August 2014, 3559 patients with WT were included in SIOP2001 trial. Among the 525 patients (15%) with metastatic WT, LR-, IR- and HR-subtypes were observed in 61 (12%), 390 (74%) and 74 (14%) patients, respectively.

Among the 74 patient with stage IV HR-WT, BT-WT subtype occurred in 34 patients (46%) and DA-WT in 40 patients (54%). The characteristics of stage IV HR-WT cohort are listed in

Table 1. Gender distribution was 1.2:1 (F:M). Median age at diagnosis was 5.5 years (range: 1.4-18.3). Local stage of the tumour was reported in 73/74 (one treatment related death before surgery) as following: stage I, II and III in 6 (8%), 19 (26%) and 48 (66%) patients, respectively. The main site of metastases was lungs (96%), which was the only involved metastatic site in 56/74 patients (76%). "Liver only" metastases were reported in 3 patients (4%). No significant differences were observed between the two HR-WT subtypes in terms of age, gender, local stage and site of metastasis. However, DA-WT had a strong trend to a higher rate of locally extended tumours (stage III) and metastases to sites other than lungs (Table 1).

First line treatment

First line treatment for each patient is reported in Supplementary Table 1.

All patients received AVD preoperative chemotherapy except two adolescents who presented with DA-WT, who had surgery before referral to a pediatric oncology department. Metastatic CR after preoperative chemotherapy was reported in 10/34 (29%) and 2/38 (5%) patients with BT-WT and DA-WT, respectively. Progressive disease (PD), mainly of metastasis, was reported during preoperative treatment in 6/38 (16%) patients with DA-WT. All patients underwent nephrectomy except one 5-year old patient with BT-WT (post-mortem evaluation) and metastatic CR who died of actinomycin D-related sinusoidal obstruction syndrome (SOS).

Among the 65 patients who did not experience PD nor toxic-death during preoperative treatment and the 2 patient who underwent upfront surgery, data on postoperative chemotherapy and local RT were available in 63/67 (94%) and 66/67 patients (98%), respectively. Fifty-eight of them (89%) started the postoperative treatment with HR regimen according to SIOP2001. Two patients with DA-WT received an alternative regimen as per

physician's choice (Ifosfamide or Cyclophosphamide + Carboplatin + Etoposide – ICE/CCE regimens) (14). For unknown reasons, 3 patients received AVD regimen (BT-WT, n=1; DA-WT, n=2), despite not being in metastatic CR. High-dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR) was administered in 6 patients (BT-WT, n=2; DA-WT, n=4) as part of first line treatment. The administered HDC consisted of: HD Melphalan 200 mg/m^2 (n=4), HD Carboplatin AUC 20 + Etoposide 1 g/m^2 + Melphalan 180 mg/m^2 (n=1), and tandem HDC with Thiotepa 720 mg/m^2 followed by HD Etoposide 1.8 g/m^2 + Melphalan 140 mg/m^2 (n=1).

Flank or abdominal RT was performed in 47/66 patients (71%), 38 stage III (BT-WT, n=18; DA-WT, n=20) and 9 stage II (BT-WT, n=4; DA-WT, n=5). Nineteen patients did not receive local RT for the following reasons: stage I (BT-WT, n= 3; DA-WT, n= 3), stage II and BT-WT (n=8), and early PD (BT-WT, n= 2; DA-WT, n= 3).

Data on m-RT were available in 63/67 patients (94%). Thirty-three patients (52%) received m-RT during first line treatment, 14 and 19 patients with BT-WT and DA-WT, respectively, regardless of the metastatic response. Median time to m-RT after surgery was 2.6 months (range: 0.5-8.6mo). Nineteen patients (BT-WT, n= 7; DA-WT, n= 12) did not receive m-RT as a first line treatment because of early postoperative metastatic progressive disease. Eleven patients (BT-WT, n= 8; DA-WT, n= 3) did not receive m-RT for unknown reasons. Among them, 6 had achieved a metastatic CR by preoperative chemotherapy alone.

Globally, all patients received their postoperative treatment with only minor dose reduction of chemotherapy whenever needed, thus suggesting good tolerance of the whole treatment.

Outcome

At the time of the analysis, 33 patients were still alive, 19/34 and 14/40 patients with BT-WT and DA-WT, respectively. The median follow-up of censored cases was of 5.1 years (95% CI,

0.3 to 9.4 years). Five-year EFS rates were 44±17% and 28±15% for BT-WT and DA-WT, respectively (p=0.09; Figure 2). Five-year OS rates were 53±17% and 29±16% for BT-WT and DA-WT, respectively (p= 0.03; Figure 3).

The outcome according to preoperative response of metastases, local treatment and postoperative treatment in BT-WT and DA-WT is reported in Figure 4 and 5, respectively.

Forty-three out of 74 patients experienced a relapse or PD. The median time to relapse after diagnosis was 7.3 months (range: 1.6-33.3) and 4.9 months (range: 0.7 -28.4) for BT-WT and DA-WT, respectively (p=0.67). Thirty-two out of 43 patients (74%) experienced a relapse/PD during treatment, 6 and 26 patients during preoperative chemotherapy and postoperative treatment, respectively. The site of relapse/progression was "lung only" in 35/43 patients (81%), "liver only" in 3/43 (7%), loco-regional in 3/43 (7%), lung and liver in 1/43, and brain in 1/43 patient (2%). For the 67 patients who did not experience PD during preoperative treatment and who were alive after surgery, the administration of m-RT during first line treatment was associated with a significantly better 5-year EFS (61±18% versus 13±13%; p<0.001, Figure 6). Excluding from the analysis those patients who experienced early postoperative progression (< 3 months after nephrectomy, n=7), the significant impact of m-RT was confirmed with a 5-year EFS of 61±18% versus 17±17% (p<0.001).

Three patients died of a treatment-related toxicity and 2nd malignancy (SOS during preoperative treatment, n=1; infection, n=1; secondary leukaemia, n=1).

In the univariate analysis, histology subtype, local stage and response of metastases after preoperative treatment had a significant impact on the outcome (Table 2, Figures 3 and 7). In the multivariate analysis, only response of metastases after preoperative treatment maintained a significant impact on survival (HR=0.3, p=0.01; Table 2).

Discussion

The SIOP2001 study is the first international prospective protocol that considered both BT after chemotherapy and DA as HR factors. While the negative impact of DA had already been established (6–9), the introduction of blastemal predominance as a new HR histologic subtype was based on retrospective observations (4,10). With the aim to increase their survival, patients with BT-WT included in the SIOP2001 protocol received an intensified treatment (HR regimen) compared to SIOP93-01 protocol where they were treated as IR-WTs.

Unfortunately, despite treatment intensification the outcome in stage IV BT-WTs is still significantly worse than those of stage IV IR-WTs enrolled in SIOP93-01 (5-year EFS of 77%, 95% CI: 71-83%) (3). The negative impact of this HR histology confirms the results of the SIOP9/GPOH trial where, among the unilateral stage I-IV WT (n=334), BT-WTs (n=25) had a 5-year progression-free survival (PFS) of 58%, slightly more than the 5-year PFS of 38% for the DA-WTs (n=21) but far from the 88% of WTs with IR histology (10).

Our current results for patients with stage IV DA-WTs are similar to those reported in patients enrolled in SIOP93-01 protocol, for whom a 5-year EFS of 33% (95% CI, 17- 64%) was reported with a similar chemotherapy regimen consisting of alternating etoposide/carboplatin and ifosfamide/epirubicin (or doxorubicin) courses for 34 weeks (maximal cumulative dose of anthracyclines of 400 mg/m^2) (3). These results are comparable to those reported by the fifth National Wilms' Tumor Study (NWTS-5) (9). Patients with stage IV DA-WT (n=24/2596) were treated with a HR regimen based on vincristine, cyclophosphamide, etoposide, doxorubicine and radiotherapy (10.8 Gy to flank/abdomen + 12 Gy to lungs). In this report 4-year EFS and OS rates of patients who received preoperative chemotherapy were 30.8% (95% CI, 9.5- 55.4%) and 44% (95%CI, 17-68%), respectively.

In our HR cohort, the prognostic value of metastatic response to preoperative treatment has been confirmed. It is important to underline that only patients with DA-WT experienced PD before surgery, and they all died of disease.

Postoperative m-RT seemed to have a significant impact on survival in our cohort. In order to take into account that some patients might have been excluded from m-RT because of early postoperative PD (selection bias), a specific analysis concerning only those patients without PD at least 3 months after nephrectomy was performed, showing that m-RT was still significantly associated with a better outcome. Considering that almost all the recurrences occurred in metastatic sites, especially in the lungs (80%), current recommendations for HR stage IV in the Umbrella SIOP-RTSG2016 protocol are to perform radiotherapy of metastatic sites for all patients as early as possible, compatibly with local radiotherapy and metastasectomy whenever indicated.

These persisting poor survival rates underline the need for new strategies. The Children's Oncology Group (COG) AREN0321 study evaluated the activity of vincristine and irinotecan in a phase 2 window in newly-diagnosed patients with stage IV DA-WTs (15). Eleven out of 14 patients (79%) had PR, and 3 had PD. The combination was well tolerated and has been incorporated into the current COG protocol for DA-WTs. The retrospective SIOP experience with irinotecan for relapsed WT was less encouraging, reporting, among the 4 DA- and 5 BT-WT, one PR in a patient with BT-WT (16).

The role of upfront HDC for these patients is still unclear. Some encouraging results have been reported in very HR settings (17–19), but no randomized study has been performed yet. In our cohort, 6 patients received HDC followed by ASCR with heterogeneous consolidation regimens, thus precluding any definitive conclusion on the matter.

Based on these data, the SIOP-RTSG 2016 Umbrella protocol suggests an intensified regimen for stage IV HR WT based on a combination of vincristine, irinotecan, cyclophosphamide, carboplatin, etoposide, and doxorubicin (5). The choice of HDC is left at the discretion of the treating physician; data on safety and outcomes will be prospectively collected.

Since 6/38 (16%) of patients with DA-WT and preoperative treatment died after having experienced PD before surgery, early identification followed by an intensified treatment seems of major importance. Somatic mutations in *TP53* are strongly associated with the development of anaplasia and with poorer survival (20). Originally thought to be pathognomonic for DA-WT (21,22), the presence of TP53 mutations in BT and even in IR histology tumours with unfavourable evolution supports the addition of TP53 screening to the diagnostic workup, as a progression/aggressive marker (22). In the future, next generation sequencing-based methods could be employed at diagnosis to screen blood for TP53 mutations, allowing early intensification of preoperative chemotherapy (21,23,24). Moreover, 1q gain, most frequent in BT-WT (25), and other potential molecular biomarkers will be prospectively assessed in the SIOP-RTSG 2016 Umbrella protocol, in order to better understand the biologic basis of resistant blastemal and DA.

In conclusion, the treatment of stage IV HR WT remains a challenge. The identification of novel agents is a priority. Collaborative research within the SIOP-RTSG and COG will offer the opportunity to develop new treatment paradigms by better understanding the biology of HR-WT.

Conflict of interest statement

The authors declare no conflict of interest.

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Legends

Figure 1. Pre-operatory and post-operatory treatment of stage IV HR WT in SIOP2001

Figure 2. Event-free survival of stage IV HR WT according to histology subtype (BT-WT versus DA-WT)

Figure 3. Overall survival of stage IV HR WT according to histology subtype (BT-WT versus DA-WT)

Figure 4. Outcome according to preoperative response and postoperative treatment in BT-WT

Figure 5. Outcome according to preoperative response and postoperative treatment in DA-WT

Figure 6. Event free survival of stage IV HR WT according to radiotherapy of metastatic sites (m-RT) as component of first line treatment

Figure 7. Overall survival of stage IV HR WT according to metastatic response to preoperative chemotherapy before surgery (complete response, CR; partial response, PR; stable disease, SD; progressive disease, PD)

Table 1. Main clinical features

Table 2. Univariate and multivariate analyses

Supplementary Table 1. First line treatment and outcome

Supplementary Table 1. First line treatment and outcome

Pt	Age (yrs)	Sex	Metastatic sites	Preoperative CT	Disease status before surgery	Histology	Local Stage	First line postoperative CT	First line local RT	Surgery M	First line m-RT	Progression/ relapse	Time to relapse/PD (mo)	Status
1#	9,1	M	Lung, Liver, Bone	AVD	PR	DA-WT	3	HRCT + HDC	Y	Y	Y	N	–	alive, FU 2.4 yrs
2#	11,3	F	Lung	AVD	PD	DA-WT	3	–	–	–	–	Y	1,5	DOD
3#	18,3	M	Lung	none	NE	DA-WT	3	HRCT + HDC	Y	N	Y	N	–	alive, FU 4.9 yrs
4#	4,6	M	Lung	AVD	PR	DA-WT	3	HRCT	Y	Y	Y	N	–	alive, FU 9.1 yrs
5#	1,8	F	Lung	AVD	CR	BT-WT	2	HRCT	N	N	N	Y	7,5	DOD
6#	2,7	F	Lung	AVD	PR	BT-WT	3	HRCT	Y	N	N	Y	2,8	alive, FU 8.5 yrs
7#	5,6	F	Lung	AVD	PR	BT-WT	1	HRCT	N	N	N	Y	6,3	DOD
8#	6,2	M	Lung	AVD	PR	BT-WT	2	HRCT + Tandem HDC	Y	Y	Y	Y	26,4	alive, FU 3.3 yrs
9#	3,8	M	Lung	AVD	PR	BT-WT	3	HRCT	Y	N	Y	N	–	alive, FU 3.5 yrs
10#	4,8	M	Liver	AVD	PD	DA-WT	3	–	–	–	–	Y	1,2	DOD
11#	4,8	M	Lung	AVD	PD	DA-WT	3	–	–	–	–	Y	1,5	DOD
12#	5,6	F	Lung, Bone	AVD	PR	BT-WT	3	HRCT + Tandem HDC	Y	N	Y	N	–	Toxic death
13#	3,8	F	Lung	AVD	SD	DA-WT	3	ICE	N	Y	N	Y	0,8	DOD
14#	4,1	F	Lung	AVD	SD	DA-WT	3	HRCT	Y	Y	N	Y	3,7	DOD
15#	6,9	M	Lung	AVD	PR	DA-WT	3	HRCT	Y	Y	N	Y	4,7	DOD
16#	4,7	M	Lung	AVD	PR	BT-WT	3	HRCT	Y	Y	N	Y	2,7	DOD
17#	9,8	M	Lung	AVD	CR	BT-WT	3	HRCT	Y	N	Y	N	–	alive, FU 6.8 yrs
18#	9,1	M	Lung	AVD	PR	DA-WT	3	HRCT	Y	N	Y	Y	6,7	DOD
19#	4,9	M	Lung	AVD	CR	BT-WT	2	HRCT	N	N	N	N	–	alive, FU 8.0 yrs
20#	15,4	M	Lung	none	NE	DA-WT	1	AVD	N	N	N	N	–	alive, FU 1.1 yrs
21#	3,0	M	Lung	AVD	CR	BT-WT	2	HRCT	Y	N	N	N	–	alive, FU 1.8 yrs
22#	3,5	F	Lung	AVD	PR	DA-WT	3	HRCT	N	Y	N	N	–	Secondary AML
23#	6,3	M	Lung	AVD	PR	DA-WT	3	HRCT	Y	N	N	Y	5,2	DOD
24#	4,4	M	Lung	AVD	PD	DA-WT	3	–	–	–	–	Y	1,2	DOD
25#	8,2	M	Lung	AVD	PR	BT-WT	3	HRCT	Y	N	Y	N	–	alive, FU 8.5 yrs
26#	4,9	F	Lung	AVD	PR	BT-WT	3	HRCT	Y	Y	Y	Y	24,0	DOD
27#	6,2	M	Lung	AVD	SD	BT-WT	1	AVD	N	N	NA	N	–	alive, FU 8.4 yrs
28#	4,9	M	Lung, Liver, Lymph nodes	AVD	PR	DA-WT	3	HRCT + HDC	Y	Y	Y	N	–	alive, FU 9.4 yrs
29#	10,5	M	Lung	AVD	SD	BT-WT	3	HRCT	Y	N	N	Y	7,4	DOD
30#	5,5	F	Lung, Liver	AVD	PD	DA-WT	2	–	–	–	–	Y	2,7	DOD
31#	3,9	M	Lung	AVD	PR	BT-WT	2	HRCT	N	N	Y	N	–	alive, FU 8.1 yrs
32#	5,8	M	Lung	AVD	CR	DA-WT	1	HRCT	N	N	Y	N	–	alive, FU 8.1 yrs
33#	3,3	F	Lung	AVD	SD	DA-WT	2	HRCT	Y	Y	N	Y	3,8	DOD
34#	5,6	M	Lung	AVD	PR	BT-WT	1	HRCT	N	Y	Y	N	–	alive, FU 6.9 yrs
35#	5,8	F	Lung	AVD	CR	BT-WT	2	HRCT	N	N	NA	N	–	alive, FU 5.2 yrs
36#	9,3	F	Lung, Liver	AVD	PR	DA-WT	3	HRCT	N	Y	N	Y	3,1	DOD
37#	3,0	F	Lung	AVD	PR	DA-WT	1	HRCT	N	Y	Y	N	–	alive, FU 5.2 yrs
38#	3,4	M	Lung	AVD	SD	BT-WT	2	HRCT	N	N	Y	N	–	alive, FU 5.1 yrs
39#	7,3	F	Lung	AVD	SD	BT-WT	3	HRCT	Y	N	N	Y	5,0	DOD
40#	7,8	F	Lung	AVD	PR	DA-WT	3	HRCT	Y	N	Y	Y	10,3	DOD
41#	5,1	M	Lung	AVD	SD	DA-WT	3	HRCT	Y	N	Y	Y	5,1	DOD
42#	3,9	F	Liver	AVD	NA	DA-WT	3	HRCT	Y	N	NA	Y	16,0	DOD
43#	13,2	F	Lung	AVD	PR	DA-WT	2	HRCT	Y	N	Y	N	–	alive, FU 1.5 yrs
44#	4,8	F	Lung, Liver	AVD	Toxic death	BT-WT	NE	–	–	–	–	N	–	Toxic death
45#	8,7	M	Lung	AVD	PR	BT-WT	2	HRCT	N	Y	Y	Y	33,3	alive, FU 2.7 yrs
46#	4,9	M	Lung	AVD	PR	DA-WT	3	HRCT	N	Y	N	Y	3,5	alive, FU 1.2 yrs
47#	5,3	F	Lung	AVD	CR	BT-WT	2	HRCT	Y	N	Y	N	–	alive, FU 2.0 yrs
48#	8,1	F	Lung	AVD	CR	DA-WT	3	CCE + HDC	Y	N	Y	Y	9,8	alive, FU 1.2 yrs
49#	3,1	F	Lung, Bone, Lymph nodes	AVD	PD	DA-WT	3	–	–	–	–	Y	1,1	DOD
50#	9,3	F	Lung, Liver	AVD	PR	DA-WT	2	HRCT	Y	Y	Y	N	–	alive, FU 3.5 yrs
51#	4,9	F	Lung	AVD	PR	BT-WT	3	HRCT	Y	N	Y	N	–	alive, FU 8.8 yrs
52#	3,4	F	Lung, Liver	AVD	CR	BT-WT	3	NA	Y	N	N	N	–	alive, FU 5.7 yrs
53#	5,6	F	Lung, Liver	AVD	CR	BT-WT	3	HRCT	Y	N	N	Y	5,9	DOD
54#	3,1	M	Lung	AVD	PR	BT-WT	2	HRCT	N	Y	N	Y	5,1	DOD
55#	7,3	M	Lung, Liver	AVD	PR	BT-WT	3	HRCT	Y	N	N	Y	13,9	DOD
56#	5,8	M	Lung	AVD	PR	BT-WT	3	HRCT	Y	Y	Y	N	–	alive, FU 0.3 yrs
57#	5,7	M	Lung	AVD	PR	DA-WT	2	HRCT	Y	Y	N	Y	7,0	DOD
58#	3,8	F	Lung	AVD	PR	DA-WT	3	HRCT	Y	N	Y	Y	8,0	DOD
59#	14,0	F	Lung	AVD	NA	BT-WT	3	HRCT	Y	N	N	Y	18,2	DOD
60#	6,0	F	Lung	AVD	NA	BT-WT	3	HRCT	Y	N	N	Y	4,4	DOD
61#	8,8	F	Lung	AVD	PR	DA-WT	3	HRCT	Y	Y	N	Y	4,1	DOD
62#	2,5	F	Lung	AVD	PR	BT-WT	2	HRCT	Y	Y	N	Y	12,1	DOD
63#	12,9	F	Lung, Liver	AVD	NA	DA-WT	3	HRCT	Y	N	N	Y	28,7	DOD
64#	5,3	F	Liver	AVD	NA	DA-WT	3	AVD	N	N	NA	Y	NA	DOD
65#	5,8	F	Lung	AVD	NA	DA-WT	3	HRCT	Y	N	Y	N	–	alive, FU 8.9 yrs
66#	4,6	F	Lung	AVD	NA	DA-WT	3	HRCT	Y	N	Y	Y	5,8	DOD
67#	6,5	M	Lung, Liver	AVD	PR	DA-WT	3	NA	Y	Y	Y	N	–	alive, FU 2.7 yrs
68#	1,4	F	Lung	AVD	NA	BT-WT	3	HRCT	Y	N	N	Y	14,2	DOD
69#	5,0	F	Lung	AVD	PR	DA-WT	3	HRCT	Y	N	Y	Y	9,3	DOD
70#	8,5	F	Lung, Liver	AVD	PR	DA-WT	2	HRCT	Y	Y	Y	Y	26,7	DOD
71#	2,6	M	Lung	AVD	CR	BT-WT	3	NA	Y	N	N	N	–	alive, FU 4.2 yrs
72#	9,3	F	Lung	AVD	NA	BT-WT	2	HRCT	N	N	Y	N	–	alive, FU 4.9 yrs
73#	2,6	F	Lung	AVD	NA	DA-WT	2	NA	NA	N	Y	N	–	alive, FU 2.4 yrs
74#	5,9	F	Lung, Liver	AVD	SD	DA-WT	3	HRCT	Y	N	N	Y	6,7	DOD

BT-WT: blastemal type wilms tumour; DA-WT: anaplastic wilms tumour; CT: chemotherapy; RT: radiotherapy; m-RT: radiotherapy of metastatic sites as first line postoperative treatment; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not available; NE: not evaluated; HRCT: high-risk chemotherapy regimen; HDC: high dose chemotherapy with autologous stem cell rescue; FU: follow-up; DOD: died of disease; AML: acute myeloid leukaemia.

Table 2: Univariate and multivariate analyses

Variable	5-yrs OS	Univariate (p)	Multivariate (HR)	Multivariate (p)
Metastatic burden (1 site vs ≥ 2)	43±14% 30±25%	0.37	-	-
Histology (BT-WT vs DA-WT)	53±17% 29±16%	0.03	1.5 (0.7-3.0)	0.30
Local stage I vs II vs III	80±35% 62±23% 29±13%	0.02	0.5 (0.2-1.1)	0.08
Preoperative metastatic response (CR vs PR/SD vs PD)	82±23% 39±16% 0%	<0.001	0.3 (0.1-0.8)	0.01

BT-WT: blastemal type wilms tumour; DA-WT: anaplastic wilms tumour; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 1. Main clinical features

	Whole cohort **n=74**	**Blastemal Type** **n=34**	**Diffuse Anaplasia** **n=40**	**p**
Median age (yrs)	5.5	5.5	5.6	0.816
Range	(1.4-18.3)	(1.4-14)	(2.6-18.3)	
Sex (Female)	41 (55%)	17 (50%)	24 (60%)	0.388
Abdominal stage (n=73)				
Stage I	6 (8%)	3 (9%)	3 (7%)	0.805
Stage II	19 (26%)	12 (36%)	7 (18%)	0.068
Stage III	48 (65%)	18 (55%)	30 (75%)	0.067
Site(s) of metastasis				
Lungs only	56 (76%)	29 (85%)	27 (68%)	0.075
Lungs + Liver	11(15%)	4 (12%)	7 (17%)	NE
Lungs + Bone	1	1	0	NE
Lungs + Liver + Bone	1	0	1	NE
Lungs + Bone + Lymph nodes	1	0	1	NE
Lungs + Liver + Lymph nodes	1	0	1	NE
Liver only	3	0	3	NE

NE: not evaluated due to low numbers; lymph nodes: extra-abdominal lymph nodes.