高 雄 榮 民 總 醫 院
威爾姆氏腫瘤診療原則

2018年02月22日 第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本共識依下列參考資料制定版本
  - 台灣兒童癌症研究群(TPOG)，TPOG_WT_ V2_20170327_

會議討論

上次會議：NA

本共識與上一版的差異

上一版	新版
1.無。	1.2018年將癌症收案對象兒童(<18歲)區分出來，故新制定兒童癌症-威爾姆氏腫瘤診療指引。

兒癌- WILMS TUMOR

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臨床診療指引　2018年第一版

◎評估

-病史、理學檢查
-營養及日常體能狀態
-胸部X光
-血液常規
-電解質及肝腎功能
-腹部超音波
-腹部電腦斷層攝影(CT)*
-胸部電腦斷層攝影(CT)*
-心臟超音波
-全身骨骼掃描(Bone scan) *

*與癌症期別相關之主要檢查

◎RISK STRATIFICATION FOR UNILATERAL WILMS TUMOR

The current therapeutic strategy for WT is based only on the post-surgical staging and histological findings [3]. The COG studies advocate for nephrectomy when feasible followed by chemotherapy. This approach allows for immediate histologic diagnosis, collection of biologic material unaltered by therapy, and accurate local staging information with histologic confirmation, such as the presence of tumor cells within lymph nodes [4]. The current generation of COG studies utilizes stage, histology, patient age, tumor weight, lung nodule response, and loss of heterozygosity (LOH) at chromosomes 1p and 16q to assign treatment groups (Table 1). The backbone of chemotherapy regimens are listed in Table 2.

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◎TABLE 1.Risk Stratification for Unilateral Renal Tumor Protocol Scheme

Patient age	Tumor weight	Stage, histology	LOH at both 1p and 16q	Rapid lung nodule response	Chemotherapy regimen	Radiation therapy
< 2 yrs	< 550 g	I, FH	Any	N/A	None	None
< 2 yrs	≥ 550 g	I, FH	None	N/A	EE4A	None
≥ 2 yrs	Any	I, FH	None	N/A	EE4A	None
Any	Any	II, FH	None	N/A	EE4A	None
Any	Any	I, FH	LOH*	N/A	DD4A	None
Any	Any	II, FH	LOH*	N/A	DD4A	None
Any	Any	III, FH	None	Any	DD4A	Local
Any	Any	III, FH	LOH*	Any	M	Local
Any	Any	IV, FH	None	Yes	DD4A	Local
Any	Any	IV, FH	None	No	M	Local, lung
Any	Any	IV, FH	LOH*	Any	M	Local, lung
Any	Any	I, FA or DA	Any	Any	DD4A	Local
Any	Any	II-III, FA	Any	Any	DD4A	Local
Any	Any	I-III CCSK	Any	Any	I	Local (RT omitted for stage I)
Any	Any	II-III, DA	Any	Any	rUH-1	Local
Any	Any	IV CCSK	Any	Any	rUH-1	Local
Any	Any	I-IV RTK	Any	Any	RTK	Local
Any	Any	IV, FA or DA	Any	Any	UH-2	Local, lung

This risk-stratification schema was modified from an existing risk stratification (Jeffrey et al 2014) and COG AREN0534.
*The detection of LOH at chromosomes 1p and 16q is optional if not applicable.

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◎TABLE 2. Chemotherapy regimens from the most recent COG studies

Regimen	Agents
EE4A	vincristine and dactinomycin
DD4A	vincristine, dactinomycin, doxorubicin and possibly radiation therapy
Regimen I	vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide
Regimen M	vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide
revised UH-1	vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide
UH2	vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, etoposide, and irinotecan
vincristine/irinotecan window therapy	vincristine and irinotecan in conjunction with revised UH-1 or UH-2 depending on response

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◎CURRENT PROGNOSTIC FACTORS

I. **Tumor stage**
The most recent modification to the NWTS/COG staging system was the reassignment of patients with "local tumor spill" from stage II to stage III based on the observation that patients with local tumor spillage have higher recurrence rates than patients without local spill [5,6]. There are several distinct clinicopathologic features that lead to a stage III designation, including lymph node involvement, tumor spillage, positive surgical margins (gross or microscopic), and peritoneal implants. The current COG and SIOP staging systems are summarized in Table 3.

II. **Histology**
Wilms tumors lacking anaplasia are designed as having "favorable histology".

III. **Patient age and tumor weight**
Historic data suggested that the subgroup of patients younger than age 2 years with small (< 550 g) stage I favorable histology tumors appears to have particularly outstanding prognosis [7]. The recently completed COG AREN0532 study readdressed the question of whether this group can be treated with nephrectomy only, and results are pending.

IV. **Completeness of lung nodule response**
Patients with complete lung nodule response had 5-year EFS and OS of 79% and 91%, patients with partial response had 5-year EFS and OS of 67% and 79%, and patients with stable or progressive disease had 5-year EFS and OS of 17% ($p = 0.011$) [8]. The COG AREN0533 study increased chemotherapy to include cyclophosphamide/etoposide in addition to vincristine/dactinomycin/doxorubicin (Regimen M) and administered lung radiation for patients with incomplete lung nodule response after 6 weeks of therapy. Patients with complete lung nodule response had therapy reduction and were continued on vincristine/dactinomycin/doxorubicin without lung radiation.

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◎ CURRENT PROGNOSTIC FACTORS

V. Loss of heterozygosity (LOH) at 1p and 16q

In the next generation of COG studies, the presence of 1p gain will be used to increase therapy intensity and its absence will be used to reduce therapy such as the potential need for radiation and doxorubicin. Concurrent LOH for chromosomes 1p and 16q, found in approximately 5% of favorable-histology Wilms tumors, was demonstrated to be significantly associated with increased relative risk (RR) of relapse and death [9].

LOH has been found in children with WT on chromosomes 11p, 16q and 1p. For the NWTS-5 study, LOH at chromosomes 11q, 16q and 1p were prospectively evaluated. The outcomes for patients with LOH at 16q and 1p were at least 10% worse than those without LOH. In the most recent COG studies, augmented therapies for LOH positive patients significantly improved overall and event free survival across all stages [10].

1 q gain was found in a review of children with WT from NWTS-4 and 5 to be a very strong predictor of relapse. This will be tested prospectively with treatment stratification based on the presence or absence of 1 q gain.

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◎TABLE 3. Staging Systems for Pediatric Renal Tumors

Stage	COG (pre-chemotherapy)	SIOP (post-chemotherapy)
I	Tumor is limited to kidney and is completely resected	Tumor limited to kidney or surrounded with fibrous pseudocapsule if outside the normal contour of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and it is completely resected (resection margins "clear")
	Renal capsule intact, not penetrated by tumor	The tumor may be protruding (bulging) into the pelvic system and "dipping" into the ureter, but it is not infiltrating their walls
	No tumor invasion of veins or lymphatics of renal sinus	The vessels of the renal sinus are not involved, but intrarenal vessel involvement may be present.
	No nodal or hematogenous metastases	Fine needle aspiration or percutaneous core needle biopsy ("tru-cut") do not upstage the tumor. The presence of necrotic tumor or chemotherapy-induced changes in the renal sinus/hilus fat and/or outside of the kidney should not be regarded as a reason for upstaging a tumor
	No prior biopsy	
	Negative margins	
II	Tumor extends beyond kidney but completely resected	The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins "clear")
	Tumor penetrates renal capsule	The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but it is completely resected
	Tumor in lymphatics or veins of renal sinus	The tumor infiltrates adjacent organs or vena cave but is completely resected
	Tumor in renal vein with margin not involved	
	No nodal or hematogenous metastases	
	Negative margin	
III	Residual tumor or nonhematogenous metastases confined to abdomen	Incomplete excision of the tumor which extends beyond resection margins (gross or microscopic tumor remains postoperatively)
	Involved abdominal nodes	Any abdominal lymph nodes are involved
	Peritoneal contamination or tumor implant	Tumor rupture before or intraoperatively (irrespective of other criteria for staging)
	Tumor spillage of any degree occurring before or	The tumor has penetrated through the peritoneal surface

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◎TABLE 3. Staging Systems for Pediatric Renal Tumors

	during surgery	
	Gross residual tumor in abdomen	Tumor implants are found on the peritoneal surface
	Biopsy of tumor (including fine needle aspiration) prior to removal of kidney	The tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon
	Resection margins involved by tumor or transection of tumor during resection (i.e. piecemeal excision of tumor)	The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery
		The presence of necrotic tumor or chemotherapy-induced changes in a lymph node or at the resection margins should be regarded as stage III
IV	Hematogenous metastases or spread beyond abdomen	Hematogenous metastases or spread beyond abdomen
V	Bilateral renal tumors Each side's tumor should be substaged separately according to the above criteria	Bilateral renal tumors Each side's tumor should be substaged separately according to the above criteria

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◎ TREATMENT PLANNING GUIDELINES

Multidisciplinary approach:

- Nephrectomy: on day 0 of week 0.
- For "biopsy only" patient, definitive surgery is undertaken at week 7 or week 13 after preoperative chemotherapy.
- Chemotherapy should be administered within 14 days post-nephrectomy.
- Week 1 = day 7 post nephrectomy.
- Newborns and all <12 months old require a reduction in chemotherapy doses to 50% of those given to older children.
- RT: over 5-7 days after nephrectomy

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◎ TREATMENT PLANNING GUIDELINES

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◎ TREATMENT PLANNING GUIDELINES

4.1 Regimen EE4A

Stage I / FH and stage II / FH: Nephrectomy, chemotherapy using Regimen EE4A

↓ reevaluate

WK	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
VCR	v	v	v	v	v	v	v	v	v	v			V*			V*			V*
AMD	v			v			v			v			v			v			v

Vincristine (VCR) 0.05 mg/kg IV push (maximum dose - 2 mg), beginning day 7 post-nephrectomy (week 1) if peristalsis has been established; then weekly for a total of 10 doses. The dose of vincristine is 1.5 mg/M^2 IV push for all patients who weigh more than 30 kg, but no single dose should exceed 2.0 mg.

Vincristine (VCR, V*) 0.067 mg/kg IV push (maximum dose - 2.0 mg) with dactinomycin at weeks 13, 16 and 19. The dose of vincristine is 2.0 mg/M^2 IV push with dactinomycin for all patients who weighed more than 30 kg, but no single dose should exceed 2.0 mg.

Dactinomycin (AMD) 0.045 mg/kg/dose IV push (maximum dose - 2.3 mg), beginning within 7 days post-nephrectomy (during week 0), and then at weeks 4, 7, 10, 13, 16, and 19. The dose of dactinomycin is 1.35 mg/M^2 for all patients who weighed more than 30 kg, but no single dose should exceed 2.3 mg.

Chemotherapy guidelines (Note: The day of nephrectomy will be considered day 0; the first dose of chemotherapy will be measured in days from that starting point.) No dose of dactinomycin should be initiated if the absolute neutrophil count is <1,000/mm^3 or the platelet count is <100,000/mm^3.

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◎ TREATMENT PLANNING GUIDELINES

4.2 Regimen DD4A
Stage III / FH; Stage I / Focal or diffuse anaplasia; Stage II or III / Focal anaplasia:
Nephrectomy, abdominal irradiation, chemotherapy using Regimen DD-4A

↓ reevaluate

WK	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
VCR	v	v	v	v	v	v	v	v	v	v			V*			V*			V*			V*			V*
AMD	v						v						v						v						v
EPI.				v						v						V*						V*			

Vincristine (VCR) 0.05 mg/kg IV push (maximum dose - 2 mg), beginning day 7 post-nephrectomy (week 1) if peristalsis has been established, then weekly for a total of 10 doses. The dose of vincristine is 1.5 mg/M^2 IV push for all patients who weighed more than 30 kg, but no single dose should exceed 2.0 mg.

Vincristine (VCR, V*) 0.067 mg/kg IV push (maximum dose - 2 mg) with dactinomycin or epirubicin at weeks 13, 16, 19, 22 and 25. The dose of vincristine is 2.0 mg/M^2 IV push for all patients who weighed more than 30 kg, but no single dose should exceed 2.0 mg.

Dactinomycin (AMD) 0.045 mg/kg/dose IV push (maximum dose - 2.3 mg), beginning within 7 days post-nephrectomy (during week 0), and then at weeks 7, 13, 19, and 25. The dose of dactinomycin administered at week 7 should be decreased by 50% (0.0225 mg/kg/dose) if whole lung or whole abdomen radiation therapy has been given. The dose of dactinomycin is 1.35 mg/M^2 for all patients who weighed more than 30 kg, but no single dose should exceed 2.3 mg. The dose of dactinomycin administered at week 7 should be decreased by 50% (0.675 mg/M^2) if whole lung or whole abdomen radiation therapy has been given.

Epirubicin (EPI) 1.5 mg/kg IV infusion over 1-2hours, is given at weeks 4 and 10; subsequently, 1.0 mg/kg IV push is given at weeks 16 and 22. The dose of epirubicin administered at week 3 should be decreased by 50% (0.75 mg/kg) if whole lung or whole abdomen radiation therapy has been given. The dose of epirubicin at weeks 4 and 10 is 45 mg/M^2 IV push, and at weeks 16 and 22 is 30 mg/M^2 IV push for all patients who weighed more than 30 kg. The dose at week 4 should be decreased by 50% (22.5 mg/M^2) if whole lung or whole abdomen radiation therapy has been given.

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◎ TREATMENT PLANNING GUIDELINES

4.3 Regimen M: modified DD-4A

a. Chest CT will be performed on all Stage IV patients with lung metastases at study enrollment and at Week 6.
b. Patients who have complete disappearance of their lung metastases (or who have tissue confirmation that the nodules do not contain viable tumor) at the Week 6 evaluation will be considered rapid responders and will continue with DD-4A.
c. Patients who do not have complete resolution of pulmonary nodules by Chest CT will undergo pulmonary irradiation and will be switched to regimen M (DD4A variation with dactinomycin and epirubicin given on the same day and alternating cyclophosphamide and etoposide)

WK	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
VCR		v	v		v	v	v			V*						V*						V*			V*
CTX^5	v			v									v						v						
$VP\text{-}16^5$	v			v									v						v						
AMD							v			v						v						v			v
EPI							v			v						v						v			v

Vincristine (VCR) 0.05mg/kg (1.5mg/M^2 if BW >30kg), iv push at weeks 8, 9, 11, 12,13. Maximal single dose is 2mg.

Vincristine (VCR, V*) 0.067mg/kg (2mg/M^2 if BW >30kg) at weeks 16, 22, 28, 31. Maximal single dose is 2mg.

Cyclophosphamide^5 (CTX^5) and Mesna with Etoposide ($VP\text{-}16^5$): days 1-5, at weeks 7, 10, 19, 25.

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Administration schedule:

-2 to 0 hr: Hydration at a rate of 200ml/M^2 /hr for 2 hours with D5 1/4 NS, IVF.

0 to 1 hr: **CTX**[5] 14.7 mg/kg (440mg/M^2 if BW >30kg) + **Mesna** 3mg/kg in 200ml/M^2 D5 1/2 NS IV infusion for 1 hour.

1-2 hr: **VP-16**[5] 3.3mg/kg in 200 ml NS /M^2 IV over 1 hr (100mg/M^2 if BW >30 kg)

3, 6, 9 hr: **Mesna** 3mg/kg (or 90mg/M^2 if BW >30kg) in 10ml NS IV infusion 15 min., q3h for 3 doses. Continue hydration at 150ml/M^2/hr for 6 hours with D5 1/2 NS

9-22 hr: D5 1/2 NS at 1000 ml/M^2 (total)

22-23 hr: same as –2 to 0 hrs.

Dactinomycin (AMD): 0.045mg/kg per dose, IV over 15 minutes. (1.35mg/M^2/dose if BW > 30 kg), (maximal single dose 2.3 mg) at weeks 13, 16, 22, 28, 31. Consider dose reduce by 50% at week 16, if delayed RT has been feasible at week 13.

Epirubicin (EPI): 1mg/kg IV in 200 ml/M^2 D5 1/2 NS, IV infusuin over 1-2 hours (30 mg/M^2 if BW >30 kg) at weeks 13, 16, 22, 28, 31. Dose should be reduced by 50% at week 16 if delayed RT has been feasible at week 13.

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◎ TREATMENT PLANNING GUIDELINES

4.4 Regimen I:
Stage I-III / Clear cell sarcoma of the kidney(CCSK) : Nephrectomy, abdominal irradiation using 1080 cGy for Stage II & III patients, whole lung irradiation for patients with pulmonary metastases, chemotherapy with vincristine, epirubicin, etoposide, cyclophosphamide and mesna using Regimen I (see below).

WK	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
VCR	v	v	v		v	v	v	v	v		v	v	V*	V*					V*						V*
EPI	v						v						v						v						v
CTX[3]							v						v						v						v
CTX[5]				v						v						v						v			
VP-16[5]				v						v						v						v			

Vincristine (VCR) 0.05 mg/kg IV push (maximum dose - 2mg.), beginning day 7 post-nephrectomy (week 1) if peristalsis has been established, then at weeks 1-3, 5-9, 11-12. The dose of VCR is 1.5 mg/M^2 IV push for all patients who weighed more than 30 kg., but no single dose should exceed 2.0 mg.

Vincristine (VCR,V*) 0.067 mg/kg IV push (maximum dose - 2 mg) at week 13, 14, 19, 25. The dose of VCR is 2.0 mg/M^2 IV push for all patients who weighed more than 30 kg., but no single dose should exceed 2.0 mg.

Epirubicin (EPI) 1.5 mg/kg IV infusion over 1-2 hours, is given at weeks 1, 7, 13, 19 and 25. The dose of EPI administered at week 7 should be decreased by 50% (0.75 mg/kg) if whole lung or whole abdomen radiation therapy has been given. The dose of EPI at weeks 1, 7, 13, 19 and 25 is 45 mg/M^2 IV push for all patients who weighed more than 30 kg. The dose at week 7 should be decreased by 50% (22.5 mg/M^2) if whole lung or whole abdomen radiation therapy has been given.

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◎ TREATMENT PLANNING GUIDELINES

Cyclophosphamide (CTX[3]) and **Mesna** on days 1-3, with **Epirubicin (EPI)** day 1, at weeks 7, 13, 19, 25.

Administration schedule:

-2 to 0 hr: Hydration at a rate of 200 ml/M^2 /hr for 2 hours with D5 1/2 NS IVF.

0 to 1 hr: **CTX[3]** 14.7 mg/kg (440 mg/M^2 if BW >30kg) + **Mesna** 3 mg/kg in 200 ml/M^2 D5/ 1/2 NS IV infusion for 1 hour.

1-2 hr: **EPI:** 1.5mg/kg IV in 200 ml/M^2 D5 1/2 NS, iv over 1-2 hours (45 mg/M^2 if BW >30kg) at day 1

if RT has been given, or at week 19 if delayed tumor resection and RT is feasible at week 13.

3, 6, 9 hr: **Mesna** 3 mg/kg (or 90 mg/M^2 if BW >30kg) in 10ml NS iv infusion 15 min., q3h for 3 doses on days 1-3. Continue hydration at 150 ml/M^2/hr for 6 hours with D5 1/2 NS.

9-22 hr: D5/½ NS at 1000 ml/M^2 (total)

22-23 hr: same as –2 to 0 hrs.

Cyclophosphamide (CTX[5]), and **Mesna** with **Etoposide(VP-16[5])** on days 1-5, at weeks 4, 10, 16, 22.

Administration schedule:

-2 to 0 hr: Hydration at a rate of 200ml/M^2 /hr for 2 hours with D5 1/4 NS, IVF.

0 to 1 hr: **CTX[5]** 14.7 mg/kg (440mg/M^2 if BW >30kg) + **Mesna** 3mg/kg in 200ml/M^2 D5 1/2 NS IV infusion for 1 hour.

1-2 hr: **VP-16[5]** 3.3 mg/kg in 200 ml NS /M^2 IV over 1 hr (100 mg/M^2 if BW >30 kg)

3, 6, 9 hr: **Mesna** 3 mg/kg (or 90 mg/M^2 if BW >30kg) in 10ml NS IV infusion 15 min., q3h for 3 doses on days 1-5. Continue hydration at150 ml/M^2 for 6 hours with D5 1/2 NS

9-22 hr: D5 1/2 NS at 1000 ml/M^2 (total).

22-23 hr: same as –2 to 0 hrs.

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◎ TREATMENT PLANNING GUIDELINES

4.5 Regimen RTK:
Stage I-IV / Rhabdoid tumor of the kidney: Nephrectomy, radiation therapy and chemotherapy with cyclophosphamide, mesna, etoposide and carboplatin

Babies <12 months of age should receive ONE-HALF of the recommended doses of all chemotherapeutic agents, as calculated on the basis of body weight. Full doses of chemotherapeutic agents should be administered to those patients when the child is ≥ 12 months of age.

WK	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
CBP[2]	v			v						v			v						v			v			
VP-16[3]	v			v						v			v						v			v			
CTX[4]							v									v									v

Carboplatin (CBP[2]) 16.7 mg/kg/day x 2 days, IV infusion over 60 minutes at weeks 1, 4, 10, 13, 19, 22. The dose of carboplatin is 500 mg/M^2/day x 2 days for all patients who weighed more than 30 kg.

Etoposide (VP-16[3]) 3.3 mg/kg/day x 3 days in 200 ml/M^2 of D5 1/2 NS as an IV infusion over 60 minutes daily is given at weeks 1, 4, 10, 13, 19, 22 after carboplatin infusion. The dose of etoposide is 100 mg/M^2/day x 3 days for all patients who weighed more than 30 kg.

Cyclophosphamide (CTX[4]) 14.7 mg/kg/day x 4 days (or 5 days) in 200 ml/M^2 of D5 1/2 NS as an IV infusion over 60 minutes daily is given at weeks 7, 16, 25. The dose of cyclophosphamide is 440 mg/M^2/day x 5 days for all patients who weighed more than 30 kg.

Mesna 3 mg/kg/dose x 4 doses in 10 ml IV over 15 minutes x 5 days, given after cyclophosphamide, at weeks 7, 16, and 25. The dose of mesna should be 90 mg/M^2/dose x 4 doses x 5 days for all patients who weighed more than 30 kg.

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◎ TREATMENT PLANNING GUIDELINES

PREOPERATIVE CHEMOTHERAPY:

Preoperative chemotherapy before nephrectomy is indicated in the following situations [11,12]:

(1) Synchronous bilateral Wilms tumor
(2) Wilms tumor in a solitary kidney
(3) Extension of tumor thrombus in the inferior vena cava above the level of the hepatic veins
(4) Tumor involved contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structures (e.g. spleen, pancreas, or colon but excluding the adrenal gland).
(5) Inoperable Wilms tumor
(6) Pulmonary compromise due to extensive pulmonary metastases

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◎ TREATMENT PLANNING GUIDELINES

4.6 Regimen VAD
Stage I-IV bilateral Wilms tumor (BWT) with biopsy revealing favorable histology or no preoperative biopsy ; stage I-III BWT with focal anaplasia ; stage I BWT with diffuse anaplasia ; or high-risk, stage III-IV unilateral Wilms tumor with contralateral nephrogenic rest or predisposition syndrome

WK	1	2	3	4	5	6
VCR	v	v	v	v	v	v
AMD	v			v		
EPI	v			v		

Vincristine (VCR): 0.05 mg/kg IV push if BW is < 30 kg; 1.5 mg/M^2 IV push if BW is > 30kg (maximal dose 2 mg) weeks 1 to 6.

Dactinomycin (AMD): 0.045mg/kg IV push over 5 minutes x 1 dose, 1.35 mg/M^2 if BW is >30kg (maximal single dose 2.3 mg) on weeks 1 and 4.

Epirubicin (EPI): 1.5mg/kg IV infusion over 1-2 hours, 45 mg/M^2 if BW is >30kg on week 1 and 4.

** Calculating drug dosage on the basis of surface area probably leads to an overestimation in infants, so doses usually are calculated according to body weight instead. However, the absence of any other severe acute toxicities (particularly neutropenia) in the current series may indicate that a 50% reduction of the dose calculated by body weight may be excessive. One option is to recommend a 33% dose reduction for children age < 6 months.
** Reduction of all drugs for infants to 2/3 of the doses for older children. (infant除了用kg算之外，還要再減少1/3的劑量)

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◎ TREATMENT PLANNING GUIDELINES

4.7 Regimen Revised UH-1
Stage IV BWT with Focal anaplasia; Stage II-IV BWT with Diffus anaplasia; Stage II or III / Diffus anaplasia; Stage IV CCSK
Nephrectomy followed by postoperative chemotherapy with revised UH-1 regimen and abdomen/flank irradiation, with a boost to residual tumor.

↓ reevaluate if primary tumor not yet resected

WK	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
VCR	v	v	v							v	v	v	v	v	v							v	v	v				v	v	v
EPI	v									v			v									v						v		
CTX[3]	v									v			v									v						v		
CBP				v			v									v			v						v					
CTX[low3]				v			v									v			v						v					
VP-16[3]				v			v									v			v						v					

Vincristine (VCR) : 0.025mg / kg for age < 1y , 0.05 mg / kg for age 1-3 yrs, 1.5mg / M^2 if age ≧3 yrs) IV over 1 minute (maximal dose 2 mg) on days 1, 8, and 15 (weeks 1-3) and weeks 10-15, 22-24, and 28-30.

Epirubicin (EPI) : 0.75 mg / kg for age < 1y , 1.5 mg / kg for age 1-3 yrs ; or 45mg/M^2 if BW > 30kg , in 200 ml/M^2 D5 1/2 NS IV infusion over 1-2 hours on day 1 (week 1) and on weeks 10, 13, 22, and 28.

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Cyclophosphamide (CTX[3]) : 14.7mg/kg, or 440mg/M^2 for BW ≧30kg in 200 ml/M^2 D5 1/2 NS IV infusion over 1 hr,-d 1,2,3 on weeks 1, 10, 13, 22, and 28.

Mesna : 20% cyclophosphamide dose at hour 0, hour 4 and hour 8 after cyclophosphamide (CTX[3]).

Carboplatin (CBP) : 500 mg/M^2 in 125-250mL D5W IV infusion over 1 hr, day 1. (For age <1y, 16.7 mg/kg) on weeks 4, 7, 16, 19, and 25.

Cyclophosphamide(CTX[low3]) : 10 mg/kg, or 300mg / M^2 if BW >30kg in 130ml /M^2 D5 1/2 NS IV over 15-30 minutes, days 1-3. on weeks 4, 7, 16, 19,and 25.

Etoposide (VP-16[3]) : 3.3mg/kg, or 100 mg / M^2 if BW >30kg in 200 ml / M^2 D5 1/2 NS IV infusion over 1 hr, days 1-3. on week 4, 7, 16, 19, and 25.

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◎ TREATMENT PLANNING GUIDELINES

4.8 Regimen UH-2

Focal or diffuse anaplastic stage IV Wilms tumor: nephrectomy followed by postoperative chemotherapy with revised UH-1 regimen, or UH-2 regimen (revised UH-1 with additional vincristine and irinotecan) in patients with poor/partial response to chemotherapy and abdomen/flank irradiation with a boost to residual tumor [13]. Patients with lung metastasis receive whole lung irradiation.

Patients whose primary tumors were initially resected undergo radiotherapy as in regimen UH-2 beginning on day 1 in week 1. Patients with delayed primary tumor resection undergo radiotherapy as in regimen UH-2 beginning on day 1 in week 7. If the primary tumor was not previously resected, patients undergo resection, if feasible, in week 7.

↓ reevaluate if primary tumor not yet resected

WK	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
VCR	v	v	v							v	v					v	v	v	v	v	v				v	v		v	v	v				v	v	v
EPI	v															v			v									v						v		
CTX[3]	v															v			v									v						v		
CBP				v			v						v									v									v					
CTX[low3]				v			v						v									v									v					
VP-16[3]				v			v						v									v									v					
IRI[5]										v	v														v	v										

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◎ TREATMENT PLANNING GUIDELINES

Vincristine (VCR) : 0.025mg / kg for age < 1y, 0.05 mg / kg for age 1-3 yrs, 1.5mg / M^2 if age ≧3 years) IV 1 minute (maximal dose 2 mg), ~~on~~ day 1 on weeks 1-3, 10, 11, 16-21, 25, 26, 28-30, and 34-36.

Epirubicin (EPI): 0.75 mg / kg for age <1y, 1.5mg / kg for age 1-3 yrs, 45mg / M^2 if BW ≧ 30kg) in 200 ml / M^2 D5 1/2 NS IV infusion over 1-2 hours, day 1 on weeks 1, 16, 19, 28, and 34.

Cyclophosphamide (CTX^3) 14.7mg/kg, or 440mg/M^2 if BW≧30kg in 200ml / M^2 D5 1/2 NS IV infusion over 1 hr, ~~on~~ days 1,2,3 on weeks 1, 16, 19, 28, and 34.

Mesna : 20% cyclophosphamide dose at hour 0, hour 4 and hour 8 after cyclophosphamide.

Carboplatine + CTX^{low} + Etoposide on the weeks 4, 7, 13, 22, 31.
Carboplatin(CBP) : 500 mg / M^2 in 125-250ml D5W, IV infusion over 1 hr, day 1. (For age <1y, 16.7 mg/kg)

Cyclophosphamide(CTX^{low3}) : 10 mg/kg in 130ml / M^2 D5 1/2 NS IV infusion over 30 minutes (300mg/M^2 if BW >30kg), ~~on~~ days 1, 2, 3.

Etoposide(VP-16^3) : 3.3 mg/kg in 200 ml/M^2 D5 1/2 NS IV infusion over 1 hr (100mg/M^2 if BW >30kg), ~~on~~ days 1, 2, 3.

Irinotecan(IRI^5) : 20 mg / M^2 / day IV infusion over 1 hr, ~~on~~ days 1-5 on the weeks 10, 11, 25, 26.

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◎ TREATMENT PLANNING GUIDELINES

- Approximately 5-7% of WT patients present with bilateral disease, either synchronously or metachronously. Bilateral WT usually occurs in younger children and more often in girls [14].
- In contrast to unilateral WT, there has not been uniform agreement about the therapeutic strategy in the management of BWT [15].
- After several multicenter trials, bilateral biopsies followed by pre-operative chemotherapy and then renal salvage surgery have been recommended. The management of BWT has evolved from primary surgery extirpation to kidney-preserving resection after preoperative chemotherapy.
- The NWTS-5 recommendation for the management of BWT includes initial biopsy and local staging followed by chemotherapy (according to abdominal stage and histological features) and second-look surgery at week 5.
- If needed, additional chemotherapy or radiation therapy is given, but definitive surgery is recommended within 12 weeks of diagnosis to limit the risk of chemoresistant clonal expansion [16].
- In recent study, radiotherapy was replaced by consolidation with high-dose melphalan and autologous hematopoietic stem cell rescue (AHSCR). They reported that on patients with BWT with pre-operative chemotherapy, late kidney-sparing surgery, and consolidation with high-dose melphalan plus AHSCR resulted in good preservation of kidney parenchymal and renal function [17].
- According to the NWTSG, metachronous bilateral WT has lower survival rates than synchronous BWT. Long-term survival rate for patients with synchronous BWT are approximately 70-80% [18].
- Survivors of BWT still have many chronic health issues and thereby need individualized long-term medical care [19]. The incidence of end-stage renal failure was 0.6% for unilateral tumors, 11.5% for BWT, and > 50% for Denys-Drash synrdrom/WAGR syndrome [20].
- Children younger than 12 months who have perilobar nephrogenic rests are at markedly increased risk of contralateral disease and require frequent and regular surveillance for several years [21].

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◎ RADIATION GUIDELINE

	Histology				
	Favorable	Focal anaplasia	Diffuse anaplasia	Clear cell sarcoma	Rhabdoid tumor
Stage I	0	10.8	10.8	10.8	10.8/19.8*
II	0	10.8	10.8	10.8	10.8/19.8*
III	10.8	10.8	19.8	10.8	10.8/19.8*
IV	Based on abdominal stage and histology				

* For patients aged > 1 year old

1. All patients except stage I and II favorable histology are irradiated.
2. Focal and diffuse anaplasia are distinguished in that Stage III diffuse anaplasia gets a higher dose
3. Whole lung RT is given only if pulmonary nodules are not in CR after week 6.
4. RT should start by day 10 post-op and not later than day 14.
5. Boost small areas of gross lung metastasis to 20 Cy.

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◎ PATIENT EVALUATION

Pretreatment Evaluation

1. Complete history and physical examination with careful notation and assessment of clinical signs relevant to Wilms tumor
2. Complete blood count, differential and platelet count
3. Chemical profile: glucose, BUN, creatinine, LDH, uric acid, Alk-P, bilirubin, SGOT, SGPT, calcium, phosphorous, sodium, potassium, total protein, and albumin
4. Urinalysis
5. Abdominal imaging
6. CT scan of chest
7. X-ray of the chest and bones
8. Bone scan for CCSK

Surgery

1. Surgical removal of involved kidney and tumor
2. Biopsy of a renal mass may be indicated if the mass is atypical by radiographic appearance for Wilms tumor, and the patient is not going to undergo immediate nephrectomy.

Genetic counseling

1. One major abnormality such as:
   Beckwith-Wiedemann symptoms (macroglossia, neonatal or postnatal macrosomia, abdominal wall defects, or visceromegaly).
2. One condition such as hemihyperplasia, overgrowth syndrome or mental retardation, aniridia, diffuse mesangial sclerosis.
3. Two or more minor malformations such as inguinal or umbilical hernia, hypospadias, renal abnormalities, ectopic testis.

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◎ FOLLOW-UP

Standard follow up for patients with Wilms tumor includes renal ultrasound and intermittent computerized tomography or magnetic resonance imaging.

Sample follow up at the end of therapy

Investigation	Time
history, physical exam	every 3 months x 8, 6 months x 4 , 12 months x 1
CBC, urinalysis, electrolytes Ca, Mg, PO4, liver enzymes total protein/albumin	every 6 months x 4, 12 months x 3
CT of the chest	every 3 months x 8 (if applicable) then switch to CXR
CXR	starting 24 months off therapy every 6 months x 4, 12 months x 1
CT/MRI of abdomen	every 3 months x 8, 6 months x 2, 12 months x 1
ECHO/ECG for stage III	either yearly or every other year depending on the regimen
CBC - complete blood count, CT - computerized tomography, CXR - plain chest radiograph, MRI - magnetic resonance imaging, ECHO - echocardiogram, ECG - electrocardiogram	

There are other specific imaging studies depending on the pathology. For example patients with clear cell sarcoma will also get scheduled for bone scans and a brain CT scan.

◎ DROP OFF CRITERIA

1. Incorrect diagnosis.
2. Patients and/or parents refuse to allow additional therapy.
3. The patient who, in the judgement of the Principal Investigator, could not or did not follow the assigned treatment, may be removed from study.
4. Patients who fail to meet all eligibility requirements of protocol (i.e., ineligible) will be taken off study, e.g., using other protocols, or not newly diagnosed patients.

◎癌症藥物停藥準則

影像學檢查，腫瘤有復發或變大情況，應停止或改變治療方式。

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