Preoperative chemotherapy combined with transcatheter arterial chemoembolization in treatment of inoperable Wilms' tumor

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Background: **Wilms' tumor is the most common malignant renal tumor in children. Nephrectomy has played a central role in the treatment of Wilms' tumor, but some advanced Wilms' tumors could not be resected immediately because of massive tumor size, involvement of vital structures, inferior vena cava invasion or distal metastasis. To improve the prognosis of patients with these inoperable Wilms' tumors, we used preoperative chemotherapy and transcatheter arterial chemoembolization (TACE) before surgery. The aim of this study was to investigate the effectiveness of preoperative therapy and to compare it with the strategy of immediate surgery.**

Methods: **Sixty-two patients with histologically confirmed advanced Wilms' tumor aged from 5 months to 10 years (mean 3.2 years) were identified from case records during the period from January 1993 to December 2002. The inclusion criteria included a volume of more than 550 ml or the mass extending beyond the midline, involvement of vital structures, inferior vena cava invasion, distal metastasis or bilateral Wilms' tumor judged by imaging studies. The patients were treated with the following 3 methods separatelly: (1) TACE with epirubicin (EPI)-lipiodol emulsion and two-week systemic chemotherapy with vincristine (VCR) and actinomycin D (ACTD) before surgery (group TACE) (31 patients); (2) conventional systemic preoperative chemotherapy with VCR, ACTD plus EPI for 4-5 weeks (group PC) (20); and (3) initial surgery (group IS) (11). In the three groups, stage Ⅱ-Ⅲ was present in 22 (71%), 16 (80%) and 9 (82%) patients; stage Ⅲ in 5 (16%), 4 (20%) and 2 (18%); stage Ⅳ in 3 (10%), 0 and 0; and stage Ⅴ in 1 (3%), 0 and 0, respectively. Unfavorable histology was found in 2, 1 and 1 patients in the three groups, respectively. Postoperative treatment for all patients was based on the postoperative stage and histology of tumors. Tumor shrinkage before operation, cases of total tumor necrosis, rate of no tumor rupture during operation, and 2-year and 4-year survival rates were compared among the 3 groups.**

Results: **In the patients treated with TACE, no drug-induced complications including cardiotoxicity, nephrotoxicity, hepatic dysfunction or bone marrow suppression were observed except for mild fever caused by tumor necrosis. Pulmonary metastases on CT disappeared in 2 of 3 patients after TACE with short-term systemic chemotherapy. The percentages of tumor size shrinkage were 32.4% and 20.3% in group TACE and group PC, respectively. No perioperative death occurred in group TACE and group PC, but two in group IS. In group TACE, only 6.5% patients experienced tumor rupture during operation in comparison with 20.0% in group PC and 45.5% in group IS. Complete surgical removal of the tumor was achieved in 27 patients (87.1%) in group TACE, significantly higher in comparison with 14 (70.0%) in group PC and 2 (18.2%) in group IS. Event-free survival (EFS) at 2 and 4 years were 87.1% (27/31) and 84.5% (11/13) in group TACE, 60.0% (12/20) and 56.3% (9/16) in group PC, 18.2% (2/11) and 18.2% (2/11) in group IS, respectively.**

Conclusions: **This study has shown that both preoperative TACE and conventional preoperative chemotherapy can be applied to properly selected patients with inoperable Wilms' tumor who are not candidates for immediate surgery. The survival rate is significantly increased in the patients undergoing preoperative TACE and short-term systemic chemotherapy compared with conventional preoperative chemotherapy and initial surgery in the same period. TACE is an effective, safe, and useful method for the initial treatment of inoperable Wilms' tumor.**

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Key words: **Wilms' tumor; preoperative chemotherapy; transcatheter arterial chemoembolization (TACE)**

Introduction

Wilms' tumor is the most common malignant renal tumor in children. Nephrectomy has played a central role in the treatment of Wilms' tumor. Some advanced Wilms' tumors could not be resected immediately because of massive tumor size, involvement of vital structures, inferior vena cava invasion or distal metastasis. Radical resection of these tumors may result in an increased risk of surgical complications. Hence, such tumors were termed "inoperable" or "unresectable" Wilms' tumor.[1-5] The challenge facing pediatric oncologists is to increase the survival rate of inoperable Wilms' tumor.

Preoperative chemotherapy has been increasingly used for patients with "inoperable" Wilms' tumor in recent years. The survival rate of the patients has been improved as a result of the advances in preoperative chemotherapy.[6-14]

Transcatheter arterial chemoembolization (TACE) has an important role in the treatment of liver tumors.[15-18] We treated patients with "inoperable" Wilms' tumor with chemotherapy and TACE before operation between 1993 and 2002. The aim of this study was to investigate the effectiveness of both chemotherapy and TACE before operation, while comparing them with initial surgery.

Methods

Patients

Sixty-two patients, (33 female and 29 male), aged from 5 months to 10 years (mean, 36 months) with Wilms' tumors unable to be resected or judged inoperable by imaging evaluation were treated at the Children's Hospital of Zhejiang University. All of them were confirmed by percutaneous needle biopsies or pathological findings of surgical specimens. Histological results were classified as unfavorable if anaplastic features were present or favorable if absent.[19]

The diagnostic criteria for inoperable tumor were massive tumor involving vital structures, intracaval extension or distal metastasis, which were judged by imaging or surgery. All the patients were divided into different pretreatment stages according to the results of the CT-determined staging system and ultrasound information[7] (Table 1). The patients with massive tumors exceeding the midline, doubtful capsular penetration or inferior vena cava invasion were included in stage Ⅱ-Ⅲ. The patients who had definite involvement of lymph nodes and diffused surgical spillage from an initial attempt to remove the tumor or peritoneal implants were defined as stage Ⅲ. The patients with lung or other distant metastases were listed in stage Ⅳ. The patients with bilateral renal tumors were classified into stage Ⅴ.

In this series, 31 patients were treated preoperatively with TACE (group TACE); 20 with preoperative chemotherapy (group PC), and 11 with initial surgery (group IS). In the three groups, stage Ⅱ-Ⅲ presented in 22 (71%), 16 (80%) and 9 (82%) patients; stage Ⅲ in 5 (16%), 4 (20%) and 2 (18%); stage Ⅳ in 3 (10%), 0 and 0; and stage Ⅴ in 1 (3%), 0 and 0, respectively. Unfavorable histology was found in 2, 1 and 1 patients in the three groups respectively. The demographics and stages at the presentation of each of group are shown in Table 2. No significant difference in age and stage distribution was noted between the three groups.

Table 1. CT-determined pretreatment staging

Ⅰ	Tumor limited to kidney within the bounds of an intact renal capusule
Ⅱ	Regional extension beyond kidney Through capsule into perirenal soft tissue Infiltrated vessels or tumor thrombus present
Ⅲ	Evidence of hilar or periaortic lymph node involvement
Ⅳ	Hematogenous metastases
Ⅴ	Bilateral renal tumors

Table 2. Demographics of patient groups

	TACE (n=31)	PC (n=20)	IS (n=11)
Age, mean (range)	3.2 (0.5-10)y	3.1 (0.8-8)y	3.3 (0.8-7)y
Sex, M:F	15:16	9:11	5:6
Stage at presentation (%)			
Ⅰ	0	0	0
Ⅱ-Ⅲ	22 (71%)	16 (80%)	9 (82%)
Ⅲ	5 (16%)	4 (20%)	2 (18%)
Ⅳ	3 (10%)	0	0
Ⅴ	1 (3%)	0	0
Postoperative stage (%)			
Ⅰ	9 (29%)	2 (10%)	0
Ⅱ	7 (23%)	4 (20%)	1 (9%)
Ⅲ	11 (35%)	14 (70%)	9 (82%)
Ⅳ	3 (10%)	0	1 (9%)
Ⅴ	1 (3%)	0	0
Histology			
FH	29	19	10
UH	2	1	1

TACE: preoperative TACE; PC: preoperative chemotherapy; IS: initial surgery; FH: favorable histology; UH: unfavorable histology.

Treatment

In group TACE, patients were subjected to transcatheter arterial chemoembolization by Seldinger's method under basal and caudal anesthesia. This procedure was performed in a standardized fashion utilizing a femoral approach. Initial angiography of the renal artery was performed to confirm the feeding artery of the tumor (Fig. 1). Then embolization emulsion consisting of iodized oil (lipiodol, Guerbet, Aulnay-Sons-B, France) 10 ml and epirubicin (EPI) 40 mg/m^2 was infused in the renal artery (Fig. 2). To treat micrometastases as early as possible, two-week systemic chemotherapy with vincristine (VCR) and actinomycin D (ACTD) was supplied to TACE for stage Ⅲ and Ⅳ patients preoperatively. Surgical resection was carried out two weeks after TACE. The patients with synchronous bilateral nephroblastoma underwent unilateral nephrectomy after preoperative TACE plus systemic chemotherapy in addition to contralateral heminephrectomy.

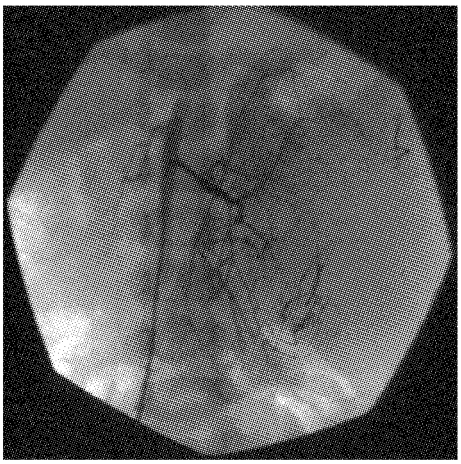

Fig. 1. Renal artery angiography confirmed the feeding artery of the Wilms' tumor in the right kidney.

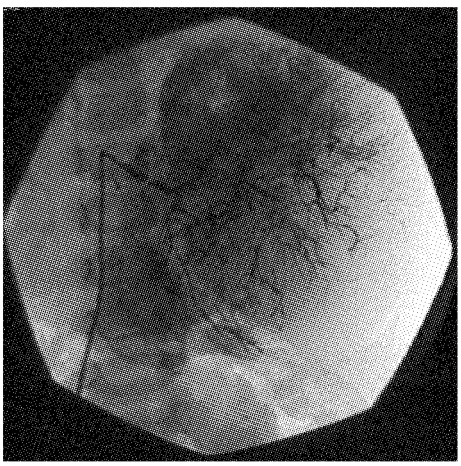

Fig. 2. The emulsion consisting of iodized oil and chemotherapeutic agents was infused in the renal artery by TACE.

In group PC, all patients received conventional systemic preoperative chemotherapy with VCR and ACTD plus EPI for 4 to 5 weeks.

In group IS, the patients underwent initial surgery after the diagnosis was confirmed.

CT scans and ultrasound/Doppler studies were performed at the presentation of the tumor and before operation. Tumor volume was measured by ultrasonograpy.

At surgery, operative stage was documented by careful inspection and enlarged lymph nodes in the renal hilum and periaortic regions were resected. The contralateral kidney was not biopsied unless bilateral disease had been demonstrated preoperatively.

Postoperative treatment of Wilms' tumor was based on tumor histology and the stage after surgery. The treatment protocol was worked out according to the NWTS-3 protocol modified by Beijing Children's Hospital.[20] Children at stage Ⅰ irrespective of histology completed a 6-month postoperative course of VCR and ACTD. For children at stages Ⅱ and Ⅲ, and with favorable histologicl results, chemotherapy was given for 15 months with VCR, ACTD and EPI. Chemotherapy with VCR, ACTD, EPI and cisplatin (DDP) was prescribed for those patients at stage Ⅳ irrespective of histology for 15 months. The radiation to the renal bed, not the whole abdomen, was added in children with favorable histological stage Ⅲ or Ⅳ tumors and unfavorable histological stage Ⅱ, Ⅲ, or Ⅳ tumors. Whole-lung radiation was not given to those patients with lung metastasis. The patients requiring renal bed irradiation received a dose of 1500 to 2000 cGy. During chemotherapy, the patients were monitored for renal and myocardial dysfunction and hearing loss. Follow-up included chest X-ray examination, abdominal ultrasonography and CT every 2-3 months. Follow-up data were available for all patients at a mean follow-up of 48 months (range, 24 to 120 months).

The results of the patients given TACE were compared with those of the patients undergoing conventional preoperative chemotherapy and initial surgery. Survival percentages were estimated as elapse or metastasis time since the diagnosis. Actuarial survival curves were generated using the Kaplan and Meier method.[21] Comparisons were made using the log-rank test. Statistical significance was considered as $P<0.05$.

Results

Response to TACE and toxicity

In the patients treated with TACE, no drug-induced complications as cardiotoxicity, nephrotoxicity, hepatic dysfunction or bone marrow suppression were observed

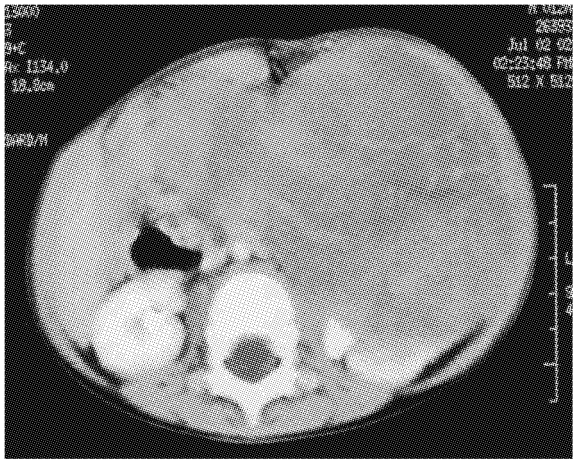

Fig. 3. A stage Ⅲ Wilms' tumor at presentation.

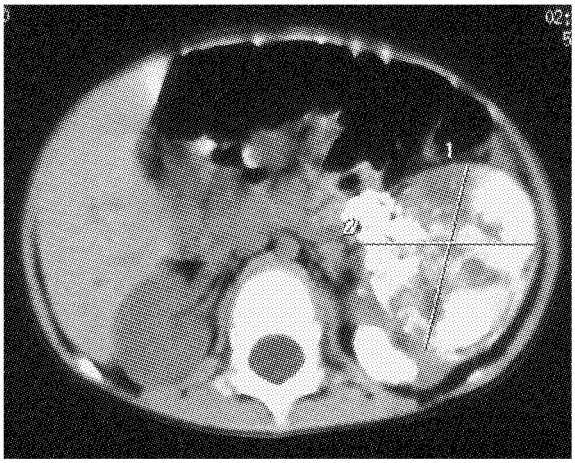

Fig. 4. Iodized oil detained in tumor after TACE by CT scan. The tumor was appreciably reduced in size.

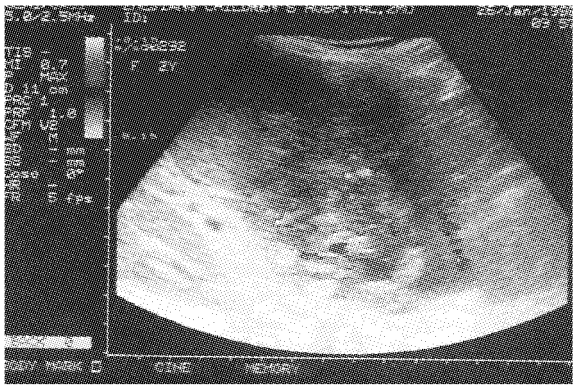

Fig. 5. Wilms' tumor before treatment, the abundant blood stream shown by Doppler ultrasonography.

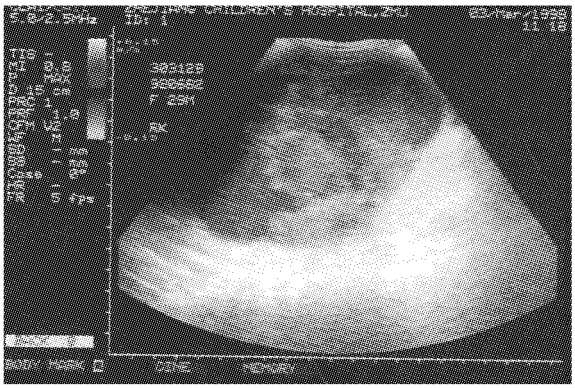

Fig. 6. The decreased perfusion of tumor after TACE (same patient as in Fig. 5).

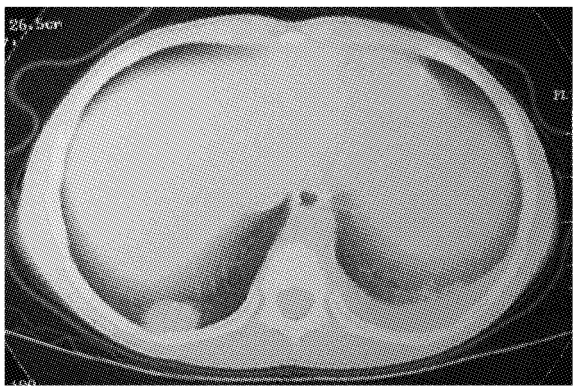

Fig. 7. One patient with stage Ⅳ Wilms' tumor. CT showing right lung metastasis and left hydrothorax.

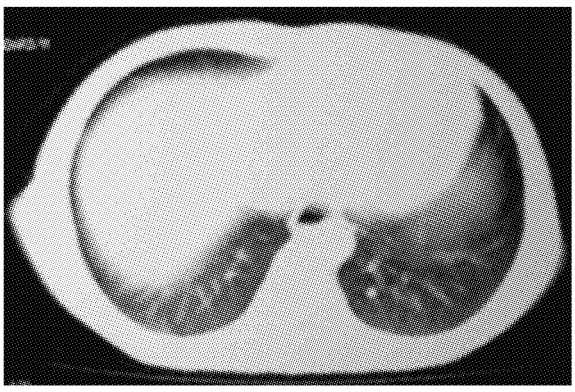

Fig. 8. Right lung metastasis and left hydrothorax disappeared after TACE combined with short course systemic chemotherapy.

except for mild fever in most cases because of tumor necrosis, which was controlled by the administration of dexamethasone. CT scan showed that iodized oil remained in tumor after TACE and the tumor size was appreciably decreased (Figs. 3,4). The decreased perfusion of tumor was shown by Doppler ultrasonography (Figs. 5,6). The general conditions of the patients were improved markedly 2 weeks after TACE. Pulmonary metastases shown by CT disappeared in 2 of 3 patients (Figs. 7,8). No tumor rupture was found before operation.

Tumor shrinkage in group TACE and group PC

Tumor shrinkage before opetation was evaluated by ultrastrasonography. The percentages of tumor shrinkage were 32.4% and 20.3% in group TACE and group PC, respectively ($P=0.0117$) (Table 3).

Table 3. Tumor shrinkage, rapture during operation, complete resection, perioperative death and tumor total necrosis in each group (%)

Group	Tumor shrinkage before operation	Rapture during operation	Complete resection of tumor	Perioperative death	Tumor total necrosis
TACE	32.4%#	2/31 (6.5)	27/31 (87.1)**	0/31 (0.0)△	7/31 (22.6)
PC	20.3%	4/20 (20.0)	14/20 (70.0)*	0/20 (0.0)△	2/20 (10.0)
IS	0.0%	5/11 (45.5)	2/11 (18.2)	2/11 (18.2)	0/11 (0.0)

#: in comparison with group PC, $P=0.0117$; **: in comparison with group PC, $P=0.03$, in comparison with group IS: $P<0.001$; *: in comparison with group IS, $P=0.029$; △: in comparison with group IS, $P=0.029$.

Table 4. Perioperative complications

Complications	Group TACE cases (%)	Group PC cases (%)	Group IS cases (%)
During operation			
Extensive hemorrhage	0	1 (5.0)	3 (27.3)
IVC injury	1 (3.2)	1 (5.0)	2 (18.2)
Death during operation	0	0	1 (9.1)
Postoperation			
Death one day after operation	0	0	1 (9.1)
Bowel adhisive obstruction	1 (3.2)	1 (5.0)	1 (9.1)
Intussusception	0	1 (5.0)	0
Wound infection	0	0	1 (9.1)

IVC: vena cava inferior.

Surgical resection

In TACE treated patients, only 6.5% (2/31) experienced tumor rupture during operation in comparison with 20.0% (4/20) of those who underwent conventional preoperative chemotherapy and 45.5% (5/11) of those who underwent initial surgery. Total removal of the tumor was achieved in 27 patients (87.1%) of group TACE, in 14 of group PC (70.0%, $P=0.03$), and in 2 of group IS (18.2%, $P<0.001$) (Table 3).

Perioperative complications are listed in Table 4. There was a marked decrease in the risk of extensive intraoperative bleeding and injury of the inferior vena cava (IVC) during operation in groups TACE and PC. No perioperative death occurred in groups TACE and PC, but two occurred during and after operation respectively in group IS.

The incidence of postoperative bowel obstruction in group TACE was similar to that of patients undergoing preoperative chemotherapy and initial surgery.

Postoperative stages

After resection, the patients were assigned to postoperative stage (Table 2). Those without pathologic evidence of capsular penetration belonged to stage Ⅰ, and those with evidence of capsular penetration or involvement of extrarenal vessels to stage Ⅱ. Those with lymph node involvement, diffused spillage from the removal of the tumor, or peritoneal implants were defined as stage Ⅲ. The patients with lung metastases at the presentation but disappeared before operation were assigned as stage Ⅳ, and those with bilateral renal tumors as stage Ⅴ.

Postoperative stages in the three groups were respectively stage Ⅰ 9 (29%), 2 (10%) and 0 patients; stage Ⅱ 7 (23%), 4(20%) and 1(9%) patients; stage Ⅲ 11 (35%), 14 (70%) and 9 (82%) patients; stage Ⅳ 3 (10%), 0 and 1 (9%) patients; and stage Ⅴ 1 (3%), 0 and 0 patients. In groups TACE and PC, downstaging of disease from stage Ⅱ to Ⅲ at presentation to postoperative stage Ⅰ was demonstrated in 9 of 22 (40.9%) and in 2 of 16 patients (12.5%) respectively. No patient was confirmed of postoperative stage Ⅰ in group IS. Six, 10 and 7 patients of stage Ⅱ and Ⅲ at presentation were confirmed in postoperative stage Ⅲ in groups TACE, PC and IS, respectively.

Pathology

In group TACE, tumor were microembolized by iodized oil and chemotherapeutic agents emulsion (Fig. 9). Pathologically specimens showed tumor necrosis was more extensive in group TACE than in group PC. Complete tumor necrosis was seen in 7 patients (22.6%) after TACE and in 2 patients (10.0%) after preoperative chemotherapy (Table 3, Fig. 10).

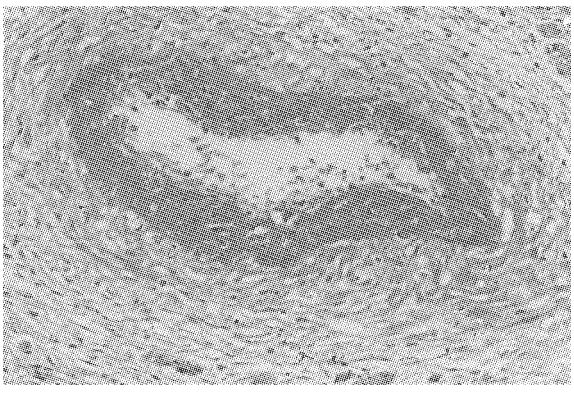

Fig. 9. Iodized oil and chemotherapeutic agents emulsion caused microembolization in the tumor.

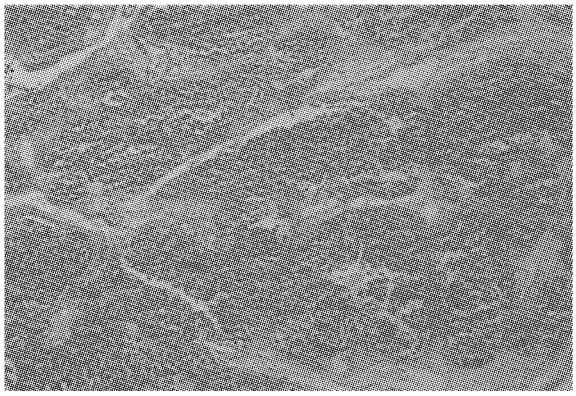

Fig. 10. Tumor complete necrosis was viewed histologically in a patient after TACE (HE 10×10).

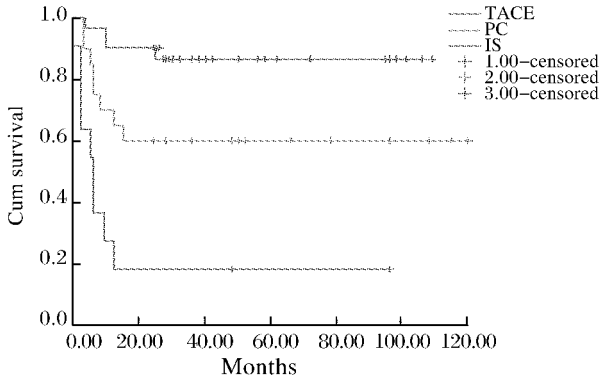

Fig. 11. Event free survival of inoperable Wilms' tumor in the three groups.

Outcomes

In group TACE, 3 patients died from pulmonary metastasis 6 to 12 months after operation. One of them had right Wilms' tumor with pulmonary and ulnaris metastases. After TACE and nephrectomy, the matastases persisted and the patient was alive with the disease for 27 months after the diagnosis.

The overall survival of group TACE was compared with that of those who had received preoperative chemotherapy and initial surgery (Table 5, Fig. 11). The 2-year event-free survival (EFS) was 87. 1% (27/31) in group TACE, 60. 0% (12/20) in group PC, and 18. 2% (2/11) in group IS. It was increased markedly in preoperatively TACE treated patients compared to those treated with preoperative chemotherapy (P = 0. 030) and initial surgery (P = 0. 000). The difference of the 2-year EFS between groups PC and IS was also significant (P = 0. 029). In the patients who had been followed up for more than 4 years, the 4-year EFS was 84. 5% (11/13) in group TACE, 56. 3% (9/16) in group PC, and 18. 2% (2/11) in group IS. The 4-year EFS was significantly increased in group TACE when compared with that of group IS (P = 0. 003).

Table 5. Survival of patient groups

Group	2 years EFS	4 years EFS
TACE	87.1% (27/31) **	84.5% (11/13) △△
PC	60.0% (12/20) *	56.3% (9/16)
IS	18.2% (2/11)	18.2% (2/11)

**: in comparison with group PC, P = 0. 030; in comparison with group IS, P = 0. 000; *: in comparison with group IS, P = 0. 029; △△: in comparison with group IS, P = 0. 003.

Discussion

Treatment of inoperable Wilms' tumor

Wilms' tumors often grow rapidly. Advanced Wilms' tumors either presented with massive involvement of vital structures or with intravascular invasion. Radical resection of tumors may cause intra-abdominal tumor spill and result in an increasing risk of surgical complications. Some of the doctors consider that these tumor are not suitable to immediate surgery and termed as "inoperable" or "unresectable" Wilms' tumor.[1-5]

Radiation therapy is one of the early adjuvant treatments when operative removal of the tumor is technically difficult. Early results with preoperative radiation have shown a decreased rate of tumor rupture and a significantly lower rate of metastases.[22,23] The introduction of dactinomycin (ACTD) in 1956 and vincristine (VCR) in the 1960s has quickly led to their use in children with inoperable Wilms' tumor.[24-26] In 1971, the International Society of Pediatric Oncology (SIOP) evaluated the effects of preoperative therapy in an attempt to decrease the morbidity and increase the survival rate in children with Wilms' tumor. Preoperative treatment was not only given to patients with tumors unable to be resected. SIOP trials showed that preoperative chemotherapy was equivalent to preoperative radiation in terms of ease of tumor removal and disease-free survival.[27] Preoperative chemotherapy has also been used for "inoperable" Wilms' tumor with an increasing frequency by NWTSG and UKCCSG in recent years.[1,3,5] The NWTSG recommends preoperative chemotherapy for patients including those with bilateral renal tumors, tumor extension into the inferior vena cava (IVC) above the hepatic veins, and those found to be inoperable at surgical exploration.[5]

Unfortunately, some patients lacked a response to preoperative treatment.[4,12] Some patients who received preoperative radiation because of lack of response to initial chemotherapy still showed no response but progressive disease and died before excision of primary tumor.[4,12] Ritchey et al[1] reviewed 131 children in NWTS-3 who had received preoperative chemotherapy for tumors unable to be resected or judged inoperable by imaging. Thirteen of them had no response to the

chemotherapy but progressive disease. Eight children died before the removal of primary tumor. Hence, clinical trials should focus on improvement of the cure rate of high-risk patients.

Since TACE is accepted as an effective and safe method for the treatment of unresectable liver tumors,[28-30] we have used it in cases of inoperable Wilms' tumor.[31]

Wilms' tumor derives blood supply from the renal artery (Fig. 1). The merits of TACE include the selective administration of agents through the renal artery and the embolism of the renal artery. Emulsion of iodized oil and other chemotherapeutic agents concentrate in the neoplastic tissue in the kidney. Iodized oil may be detained in tumor to increase contact time of chemotherapeutic agents, and induce tumor ischemia and microembolization and necrosis of the tumor. This approach makes tumor cells directly exposed to high-concentration agents, while avoiding concomitant systemic toxicity.

Preoperative TACE for the treatment of inoperable Wilms' tumor will increase the rate of complete resection and decrease the operative mortality. In most cases, the tumor is appreciably reduced in size after TACE. Being smaller, less friable, and easier to remove, it has a decreased risk of extensive intraoperative bleeding and complications. The low morbidity and zero mortality for nephrectomy after TACE is a noteworthy result of inoperable Wilms' tumor. In the present study the patients who had had preoperative TACE showed a better disease-free survival rate than those who had not. The acute toxicity and late effects of TACE are minimimal and do not jeopardize the disease-free survival rate.

In Europe and many other parts of the world, the SIOP protocols are used for the treatment of advanced Wilms' tumor. The SIOP study showed that the patients with favorable histology in all stages have a survival rate of >90%. The method of TACE is primarily applied in China, with a relatively lower survival rate than the SIOP reported. It might be owing to some patients with anaplasia (UH) in the group and the postoperative therapy in some patients is inadequate due to downstaging.

Experience in SIOP has shown that maximal shrinkage occurs after 4 to 6 weeks of preoperative chemotherapy.[10] In our study the maximal shrinkage of the tumor and the improvement of patients' general condition occurred 2 weeks after TACE. Therefore, nephrectomy should be performed 2 weeks after TACE when the tumor has shrunk and necrosed as much as possible.

TACE is safe but needs monitoring and intensive care. We encourage intravenous hydration and alkalization during the procedure.

TACE is considered effective only for primary lesion and is less likely to be effective against distant metastasis. With short-term preoperative systemic chemotherapy, the procedure may result in shrinkage of tumor parenchyma and disappearance of metastatic lesions. Its combination with systematic chemotherapy should be more effective to control or destroy the lesions out of the kidney, especially in patients with tumor thrombus in the vena cava, involvement of periaortic lymph node or distal metastasis.

In conclusion, both preoperative TACE and chemotherapy can be applied to properly selected patients with inoperable Wilms' tumor who are not candidates for immediate surgery. The survival rate is significantly increased in patients undergoing TACE compared with preoperative chemotherapy and initial surgery in the same period. TACE is an effective, safe, and useful method for the initial treatment of inoperable Wilms' tumor. TACE combined with short-term preoperative systematic chemotherapy should be considered effective to shrink tumor size and to destroy the lesions out of the kidney. Clinical trials should be continued to improve the cure rate of the high-risk patients with this tumor.

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Competing interest: No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.
Contributors: LMJ wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version. LMJ is the guarantor.

References

1 Ritchey ML, Pringle KC, Breslow NE, Takashima J, Moksness J. Management and outcome of inoperable Wilms' tumor. A report of National Wilms Tumor Study-3. Ann Surg 1994;220:683-690.
2 Oue T, Kubota A, Okuyama H, Kawahara H, Inoue M, Yagi K, et al. Megatherapy with hematopoietic stem cell rescue as a preoperative treatment in unresectable pediatric malignancies. J Pediatr Surg 2003;38:130-133.
3 Grundy RG, Hutton C, Middleton H, Imeson J, Pritchard J, Kelsey A, et al. Outcome of patients with stage III or inoperable WT treated on the second United Kingdom WT protocol (UKWT2); a United Kingdom Children's Cancer Study Group (UKCCSG) study. Pediatr Blood Cancer 2004;42:311-319.
4 Mahmood A, Ghafoor T, Badsha S. Wilms' tumour: presentation and treatment. J Coll Physicians Surg Pak 2004;14:142-145.
5 Ritchey ML. The role of preoperative chemotherapy for Wilms' tumor: the NWTSG perspective. National Wilms'

Tumor Study Group. Semin Urol Oncol 1999;17:21-27.
6 de Kraker J, Lemerle J, Voute PA, Zucker JM, Tournade MF, Carli M. Wilms' tumor with pulmonary metastases at diagnosis: the significance of primary chemotherapy. International Society of Pediatric Oncology Nephroblastoma Trial and Study Committee. Clin Oncol 1990;8:1187-1190.
7 Greenberg M, Burnweit C, Filler R, Weitzman S, Sohl H, Chan H, et al. Preoperative chemotherapy for children with Wilms' tumor. J Pediatr Surg 1991;26:949-953.
8 Dykes EH, Marwaha RK, Dicks-Mireaux C, Sams V, Risdon RA, Duffy PG, et al. Risks and benefits of percutaneous biopsy and primary chemotherapy in advanced Wilms' tumour. J Pediatr Surg 1991;26:610-612.
9 Capra ML, Walker DA, Mohammed WM, Kapila L, Barbor PR, Sokal M, et al. Wilms' tumor: a 25-year review of the role of preoperative chemotherapy. J Pediatr Surg 1999;34:579-582.
10 Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000;27:443-454.
11 Zhao YB, Zheng SB, Mao XM, Zhou HK, Zhang P. Clinical effects of preoperative chemotherapy for Wilms' tumor. Di Yi Jun Yi Da Xue Xue Bao 2004;24:722-724.
12 Reinhard H, Semler O, Burger D, Bode U, Flentje M, Gobel U, et al. Results of the SIOP 93-01/GPOH trial and study for the treatment of patients with unilateral nonmetastatic Wilms' Tumor. Klin Padiatr 2004;216:132-140.
13 Graf N, Semler O, Reinhard H. Prognosis of Wilms' tumor in the course of the SIOP trials and studies. Urologe A 2004;43:421-428.
14 Grundy RG, Hutton C, Middleton H, Imeson J, Pritchard J, Kelsey A, et al. Outcome of patients with stage III or inoperable WT treated on the second United Kingdom WT protocol (UKWT2); a United Kingdom Children's Cancer Study Group (UKCCSG) study. Pediatr Blood Cancer 2004;42:311-319.
15 Berthold F, Schultheis KH, Aigner K, Lampert F. Combination chemotherapy and chemoembolization in the treatment of primary inoperable hepatoblastoma. Klin Padiatr 1986;198:257-261.
16 Oue T, Fukuzawa M, Kusafuka T, Kohmoto Y, Okada A, Imura K. Transcatheter arterial chemoembolization in the treatment of hepatoblastoma. J Pediatr Surg 1998;33:1771-1775.
17 Malogolowkin MH, Stanley P, Steele DA, Ortega JA. Feasibility and toxicity of chemoembolization for children with liver tumors. J Clin Oncol 2000;18:1279-1284.
18 Arcement CM, Towbin RB, Meza MP, Gerber DA, Kaye RD, Mazariegos GV, et al. Intrahepatic chemoembolization in unresectable pediatric liver malignancies. Pediatr Radiol 2000;30:779-785.
19 Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms' tumors: results from the First National Wilms' Tumor Study. Cancer 1978;41:1937-1948.
20 Bai JW. Wilms' Tumor. In: Zhang JZ, eds. Modern Pediatric Oncologic Surgery. Beijing: Beijing Science Publishing House, 2003:245-254.
21 Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958,53:456-481.
22 Friedlander A. Sarcoma of the kidney treated by the roentgen ray. Am J Dis Child 1916;2:328-330.
23 Nesbit RM, Adams FM. Wilms' tumor. J Pediatr 1946;29:295-303.
24 Sullivan MP, Sutow WW, Cangir A, Taylor G. Vincristine sulfate in management of Wilms' tumor. JAMA 1967;202:381-384.
25 Wagget J, Koop CE. Wilms' tumor preoperative radiotherapy and chemotherapy in the management of massive tumors. Cancer 1970;26:338-340.
26 Bracken RB, Sutow WW, Jaffe N, Ayala A, Guarda L. Preoperative chemotherapy for Wilms' tumor. Urology 1982;19:55-60.
27 Leape LL, Breslow NE, Bishop HC. The surgical treatment of Wilms' tumor: results of the National Wilms' Tumor Study. Ann Surg 1978;187:351-356.
28 Oue T, Fukuzawa M, Kusafuka T, Kohmoto Y, Okada A, Imura K. Transcatheter arterial chemoembolization in the treatment of hepatoblastoma. J Pediatr Surg 1998;33:1771-1775.
29 Han YM, Park HH, Lee JM, Kim JC, Hwang PH, Lee DK, et al. Effectiveness of preoperative transarterial chemoembolization in presumed inoperable hepatoblastoma. Vasc Interv Radiol 1999;10:1275-1280.
30 Arcement CM, Towbin RB, Meza MP, Gerber DA, Kaye RD, Mazariegos GV, et al. Intrahepatic chemoembolization in unresectable pediatric liver malignancies. Pediatr Radiol 2000;30:779-785.
31 Li MJ, Zhou YB, Shen LG. Prospective study of preoperative transcatheter arterial chemoembolization for Wilms' tumor. Zhejiang Da Xue Xue Bao Yi Xue Ban 2003;32:69-71.

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