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Management and Outcome of Inoperable Wilms Tumor

A Report of National Wilms Tumor Study-3

Michael L. Ritchey, M.D.,* Kevin C. Pringle, M.D.,† Norman E. Breslow, Ph.D.,‡ Janice Takashima,§ Jami Moksness,‡ Craig W. Zuppan, M.D.,‖ J. Bruce Beckwith, M.D.,‖ Patrick R. M. Thomas, M.D.,¶ and Panayotis P. Kelalis, M.D.#

From the Division of Pediatric Surgery, University of Texas, Houston, Texas; the Department of Surgery,† University of Otago, Wellington, New Zealand; the Department of Biostatistics,‡ University of Washington, Seattle, Washington; the Data and Statistical Center,§ Seattle, Washington; the Division of Pediatric Pathology,‖ Loma Linda University, Loma Linda, California; the Department of Radiation Oncology,¶ Temple University, Philadelphia, Pennsylvania; and the Department of Urology,# Mayo Clinic, Jacksonville, Florida*

Methods

The authors reviewed 131 children enrolled in National Wilms Tumor Study-3 (NWTS-3) who received preoperative treatment for tumors unable to be resected at surgery or judged inoperable by imaging evaluation. Preoperative biopsies were performed on 103 patients. Patients were assigned a pretreatment stage: stage II (11 patients), stage III (39 patients), stage IV (66 patients), and unknown (15 patients). The chemotherapy regimen included dactinomycin and vincristine (81 patients), dactinomycin, vincristine, and doxorubicin (30 patients), dactinomycin, vincristine, doxorubicin, and cyclophosphamide (10 patients), and other (8 patients). Preoperative radiation therapy was started concurrently with chemotherapy (27 patients) or because of lack of response (14 patients). Two patients were given preoperative irradiation without chemotherapy.

Results

Response to therapy was assessed after the first trial of chemotherapy. Partial responses were noted in 110 patients (85%), 3 had complete responses, 13 had no response or progression of disease, and 5 patients were not able to be evaluated. There were no significant differences in preoperative response to the different chemotherapy regimens. Median time interval from diagnosis to nephrectomy was 58.5 days. When compared with NWTS-3 patients not receiving preoperative treatment, survival was reduced for patients treated preoperatively (88% *vs.* 74%, respectively, 4-year survival), which was only partially explained by differences in stage distribution. Median duration of follow-up was 5.9 years. Lack of response to the preoperative treatment was associated with a poor prognosis. Eight children died before removal of the primary tumor. All eight had either progressive disease or no response to the preoperative treatment.

Conclusions

The use of preoperative treatment can facilitate subsequent surgical resection in selected patients with inoperable Wilms tumors. Although these very large tumors—judged unable to be resected—have a somewhat worse prognosis, nephrectomy was completed in 93% of patients after preoperative treatment. However, preoperative treatment will lead to less accurate surgical and pathologic staging, and undertreatment should be avoided in these high-risk patients.

Wilms tumors can grow rapidly and are large in proportion to the child's body habitus. However, most children with nephroblastoma can be treated with primary nephrectomy, according to the current recommendation of the National Wilms Tumor Study (NWTS).[1] Occasionally, the surgeon will encounter an enormous tumor that may involve vital structures, which is not amenable to primary excision. Attempted radical resection with en bloc removal of surrounding organs can result in an increased risk of surgical complications.[2] There have been several reports in which preoperative chemotherapy or radiation therapy were used to reduce the tumor burden in children with massive tumors thought to be too large for primary excision.[3–5] However, the number of patients reported in these studies has been small, making it difficult to draw firm conclusions regarding the effect of preoperative management of such children on patient survival. This review reports on all children enrolled in NWTS-3 who received preoperative chemotherapy or radiation therapy for inoperable tumors.

METHODS

The Third National Wilms Tumor Study (NWTS) enrolled 2496 patients from May 1979 to April 1986[1]; 136 children with unilateral tumors received preoperative chemotherapy or radiation therapy and are the subject of this review. Five of the 136 were excluded, leaving 131 for analysis. Reasons for exclusion included pathologic diagnosis other than Wilms tumor (two patients), or incomplete records. The NWTS-3 patients who underwent primary nephrectomies and were treated according to one of the NWTS treatment regimens were used for comparison. Children receiving preoperative chemotherapy for bilateral tumors are not included in this review. The clinical records that were analyzed included checklists completed by the operating surgeon, operative reports, pathology reports and checklists, chemotherapy and radiation therapy summaries, and flow sheets that detailed patient treatment.

The median age at diagnosis for the 131 patients was 52 months; only two patients were younger than 1 year of age. The median duration of follow-up was 5.9 years. There was an equal distribution of patients by sex (62 males, 69 females). The right kidney was involved in 74 children, and the left kidney was involved in 57.

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Address reprint requests to Michael Ritchey, M.D., Division of Pediatric Surgery, 6431 Fannin, Suite 6.264, Houston, TX 77030.

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The basis for preoperative treatment of the tumor was as follows: tumor found unable to be resected at surgical exploration (69 patients), tumor judged to be inoperable by clinical evaluation or imaging studies (51 patients), extensive intravascular tumor extension (5 patients), and other reasons (respiratory distress, etc., 6 patients).

Patients were assigned to a pretreatment stage following the NWTS system, based on all available information.[6] Eleven patients were assigned as stage II, based on local tumor spill from biopsies, capsular penetration or involvement of the extrarenal vessels. Thirty-nine patients were classified as stage III because of lymph node involvement, diffuse surgical spillage from the initial attempt to remove the tumor, or peritoneal implants. Because all patients had tumors incompletely removed before treatment, this was not used as a criterion for stage III disease. Only those patients with massive tumors judged unable to be resected at surgical exploration were classified stage III, in the absence of other established criteria. There were 66 stage IV patients with tumor involvement of lung (57 patients), liver (22 patients), or other distant metastases (5 patients). Intracaval tumors were present in 28 patients, with right atrial extension in two children. Fifteen patients could not be assigned a pretreatment stage because of incomplete information.

With the exception of two children, all patients received preoperative chemotherapy. Biopsies were performed for diagnosis in 103 children; needle biopsies were done for 21 children and open biopsies were done for 82. Most patients were given a combination of dactinomycin and vincristine (81 patients), or dactinomycin, vincristine, and doxorubicin (30 patients). Most patients given more than two drugs had stage III or IV disease. The duration of preoperative treatment was variable; 17 children were treated for less than 30 days, 44 were treated for 30 to 60 days, and 61 were treated for more than 60 days. Preoperative radiation therapy (XRT) was given to 43 children. Radiation therapy was started concurrently with the chemotherapy in 27, but in 14 patients, it followed chemotherapy and was given because of a lack of response. Two patients were given preoperative XRT alone without chemotherapy. The amount of abdominal irradiation varied—<1500 cGy (20 patients), 1500–2500 cGy (16 patients), 2501–3500 cGy (6 patients), and> 3500 cGy (1 patient). In 11 patients, treatment was given to the whole abdomen; the remaining 32 patients received flank or tumor bed irradiation only. Ten children received whole lung irradiation preoperatively to treat pulmonary metastases.

Survival percentages were estimated as a function of elapsed time since diagnosis using standard actuarial methods.[7] The statistical significance of the differences between survival curves was evaluated using stratified and nonstratified versions of the log-rank test.[8] Survival

Table 1. RESPONSE AFTER FIRST TRIAL OF CHEMOTHERAPY

	PD	NR	PR	CR	Inevaluable
Unknown chemotherapy			2		1
VCR		1	3		
VCR + ADR			1		
AMD + VCR	5	5	69		2
AMD + VCR + ADR		1	27	2	
AMD + VCR + ADR + CPM		1	8	1	
Total	5	8	110	3	3 (129)*

* Two patients were treated with preoperative radiation therapy and did not receive preoperative chemotherapy.
PD = progressive disease; NR = no response; PR = partial response; CR = complete response; VCR = vincristine; ADR = doxorubicin; AMD = dactinomycin; CPM = cyclophosphamide.

comparisons, for patients classified by clinical response, measured elapsed time from the date the response was evaluated.

RESULTS

Results of the 131 patients given preoperative therapy were compared with the 1981 randomized (i.e., randomized for treatment after primary nephrectomy) or followed[1] (e.g., patients not randomized, but treated according to one of the NWTS treatment regimens) children undergoing primary nephrectomies for unilateral Wilms tumors. The children undergoing preoperative treatment were substantially older, with 61% older than 4 years of age at diagnosis, compared with 35% of those undergoing primary nephrectomies. The preoperative patients had a much less favorable stage distribution. Forty-seven percent were stage IV, which is considerably higher than the 12.3% of patients undergoing primary nephrectomies.

Response to therapy was assessed after the first trial of chemotherapy and correlated with the chemotherapy regimen received (Table 1). Response was categorized as progressive disease, no response, partial response, and complete response. For this analysis, response of the primary tumor or metastatic deposits was considered. Partial response was defined as any measurable reduction in size of the primary tumor or metastasis. Information used to define response included imaging studies and clinical assessment of tumor size. There was a small difference in response for patients receiving dactinomycin and vincristine (83% response) compared with those receiving dactinomycin, vincristine, and doxorubicin (95%), but these differences lack statistical significance.

The reduction in size of the primary tumor also was determined by review of both the imaging studies and the surgeon's assessment. Response of the primary tumor was assessed after all preoperative treatment had been received. Ninety-three patients (71%) had greater than 23% reduction in the size of the primary tumor. Of the 14 children receiving preoperative radiation because of a lack of response to the initial course of chemotherapy, 10 subsequently had a partial response, 3 had progressive disease, and 1 was not evaluable.

Response to the first trial of chemotherapy correlated with patient survival (Table 2). All five children with progression of disease during the initial course of therapy died of tumors, and three of eight with no appreciable response also died. The median interval from diagnosis of Wilms tumor to nephrectomy was 58.5 days; it was less than 30 days in 17 children, 30 to 59 days in 46 children, and more than 60 days in 59 children. Eight children died before excision of the primary tumor could be performed. All of these patients had either progressive disease or no response to the preoperative treatment. One patient was unable to be observed for follow-up, and it is unknown if surgery was performed.

Patients were assigned to a pathologic stage after surgical resection. There was "downstaging" of the tumor in most patients, as has been noted in the International Society of Pediatric Oncology (SIOP) trials.[9] Correlation with preresection stage is shown in Table 3. Eleven patients could not be assigned a final stage because of incomplete information; this included eight children who died before definitive resection. Soilage from surgical spill was decreased in patients receiving preoperative treatment compared with those children undergoing primary nephrectomies—i.e., local (3.1% *vs.* 11.1%) and diffuse spill (1.5% *vs.* 3.1%). The incidence of preopera-

Table 2. CORRELATION OF SURVIVAL WITH CLINICAL RESPONSE AFTER FIRST TRIAL OF CHEMOTHERAPY

		Deaths			
	n	Observed	Expected	% Alive 2 yrs	% Alive 4 yrs
Clinical response					
PD	5	5	0.4	0.0	0.0
NR	8	3	1.9	62.5	62.5
PR	107	24	28.8	85.8	79.0
CR	3	0	0.9	100.0	100.0
		p = 0.0001			

PD = progressive disease; NR = no response; PR = partial response; CR = complete response.
Survival status is unknown for two patients. Clinical response after initial course of treatment is inevaluable for five patients. One patient died before clinical response evaluated. Time is calculated from date response evaluated.

Table 3. CORRELATION OF PREOPERATIVE STAGE AND PATHOLOGIC STAGE AFTER SURGERY

		Stage After Excision of Tumor*				
	n	N/A†	I	II	III	IV
Preoperative Stage						
N/A	15	1	9	2	3	
II	11		6	3	2	
III	39	4	8	7	20	
IV	66	6	16	9	17	18
Total	131	11	39	21	42	18

* Post-treatment stage was calculated based on measurable disease at the time of excision and extent of viable tumor.

† N/A Stage assignment could not be made due to missing data. Eight of the 11 patients that do not have postoperative stage died before nephrectomy was performed.

tive tumor rupture was not decreased (6.2% *vs.* 5.1%) in comparison with NWTS children undergoing primary nephrectomies.

Overall, postoperative complications were encountered in 25 of the 131 patients (19%). These are listed in Table 4. The incidence of bowel obstruction was similar to results in patients undergoing primary nephrectomies.[2] Two children had complications after initial explorations and biopsies of the tumors. All other patients endured complications after definitive resections of the tumors. The overall incidence of complications is similar to that of children undergoing primary nephrectomies for Wilms tumors,[2] despite having very large tumors unable to be resected at initial presentation. Intracaval extension was present in 23% of the preoperative patients, which is several times the expected incidence. Fifteen children underwent en bloc resections of other organs at the time of nephrectomy. These are all adverse variables known to increase the risk of surgical complications significantly,[2] suggesting that preoperative treatment facilitated subsequent surgical removal.

Postoperative chemotherapy was given to all the children, with the exception of three who were found to have no viable tumor in the operative specimen. Eighty children received postoperative XRT. This included whole lung irradiation in 33 patients and abdominal irradiation in 75 patients—<1500 cGy (15 patients), 1500–2500 cGy (54 patients), 2501–3500 cGy (4 patients), and >3500 cGy (2 patients). In 16 patients, treatment was given to the whole abdomen; the remaining 59 patients received tumor bed irradiation. There were only 11 children who did not receive irradiation preoperatively or postoperatively. This represents a higher proportion of patients receiving XRT than those randomized or observed for follow-up in NWTS-3. Information regarding the radiation treatment was not available for five children.

Pathology

The histology of 119 cases was reviewed by the NWTS Pathology Center and has been reported previously.[10] There were 83 patients in whom pathologic material from the definitive operation was available for review. Thirty-eight also had slides from the original biopsy material for comparison. Pretreatment biopsy slides alone were available for 36 other patients. Anaplasia was present in 11 of the 119 (9.2%), and the remaining 108 cases were Wilms tumors of favorable histology. The proportion of patients with unfavorable histology is higher than for the group of NWTS-3 patients undergoing primary nephrectomies,[1] but is similar when corrected for age and stage. More than half of the preoperative patients were older than 4 years of age at diagnosis, and half of the patients had stage IV disease.

There were four patients (11% of patients with both pretreatment biopsy and nephrectomy specimens available for review) with discordance between the pathology of the preoperative biopsy and the final pathology of the resected specimen. The original classification was favorable histology, but anaplasia was present in the nephrectomy specimens. In all cases with anaplasia in the initial biopsy specimen, anaplasia was identified in the nephrectomy specimen.

The mean weight of the tumors was 365 g (median = 220 g), which is smaller than tumors from patients treated with primary nephrectomies for whom the mean weight was 617 g (median = 510 g). This reflects the influence of the preoperative therapy on reducing the tumor size.

Survival

Overall, survival based on pretreatment stage was reduced for preoperatively treated patients as compared

Table 4. SURGICAL COMPLICATIONS

	No. of Patients	Percent
Bowel obstruction	10	(7.6)
Wound infection	7	(5.3)
Extensive hemorrhage	5	(3.8)
Hypotension	1	(0.8)
Postoperative bleeding	1	(0.8)
Cardiac arrest	2	(1.5)
IVC obstruction	1	(0.8)
Splenic injury	1	(0.8)
Other	7	(5.3)

Table 5. SURVIVAL BY PRETREATMENT STAGE

	n	Deaths		% Alive 2 yrs	% Alive 4 yrs
		Observed	Expected		
Stage I–II					
Preoperative	11	1	0.8	100.0	100.0
Nonpreoperative	1259	86	86.2	96.3	93.8
		(p = 0.80)			
Stage III					
Preoperative	38	10	7.2	81.6	76.3
Nonpreoperative	475	89	91.8	87.4	83.4
		(p = 0.29)			
Stage IV					
Preoperative	62	22	16.7	69.1	64.1
Nonpreoperative	247	66	71.3	78.5	74.2
		(p = 0.15)			
Total					
Preoperative	111*	33	24.7		
Nonpreoperative	1981	241	249.3		
		(p = 0.07)			
Overall survival					
Preoperative	130†	35	15.5	79.8	74.2
Nonpreoperative	1981	241	260.5	91.9	88.8
		(p = 0.0001)			

* Patients in whom pre-treatment stage information was not available were excluded.
† One patient in whom survival data was not available was excluded.

with those treated by initial nephrectomy (Table 5). This difference is explained only partially by differences in stage distribution. Although there was a slightly higher response rate (complete or partial) preoperatively if three chemotherapeutic agents were administered *versus* two drugs (95% *vs.* 83%), there was no difference in survival when comparing these regimens stratified by histology and stage. There also was no difference in survival in patients judged to be inoperable by imaging studies alone compared with those determined unable to be resected at surgery.

Evaluating the effect of preoperative XRT to the primary tumor on survival was difficult because of the delay in starting XRT in some patients and its use in patients who had failed an initial trial of chemotherapy. We compared outcomes among patients who received XRT during the first 3 weeks of treatment (no one receiving radiation in conjunction with the initial trial of chemotherapy started XRT after this number of days) compared with those patients who did not receive preoperative XRT, excluding those patients who relapsed or died during this period. The children receiving XRT appeared to fare worse. However, when the comparison was restricted to patients who received XRT in conjunction with the trial of chemotherapy, excluding those irradiated because they failed to show a response to the initial chemotherapy, the differences were not significant (p = 0.21).

Survival based on post-treatment stage also was analyzed in an attempt to determine if treatment based on the postchemotherapy stage might lead to undertreatment. For the purpose of this analysis, stage IV patients were excluded because these patients should be treated as stage IV disease irrespective of the findings after treatment. Only 56 patients were available for analysis. There was an observed difference in survival for "post-treatment stage I," the latter patients fared worse (85.6% *vs.* 96.7%, p = 0.02). Overall there was no difference in survival (p = 0.55). These figures must be interpreted with caution because of the small numbers of patients in each group. Additionally, the treatment regimens and duration of treatment for the preoperative patients were not standardized, which could have an impact on outcome. It was apparent that the clinicians were not basing treatment given postoperatively on postchemotherapy stage alone. The majority of patients with either stage II or III disease received doxorubicin or abdominal irradiation as part of their therapy.

The percentage of viable tumor in the nephrectomy specimen was found to correlate with survival. Survival at 4 years exceeded 90% if there was <10% viable tumor. It was 80% if there was 10% to 50% viable tumor, and it was only 47% if there was greater than 50% viable tumor (p = 0.0001). The location of viable tumor also was a significant factor in determining outcome with im-

proved survival when viable tumor was not present outside the kidney (viable stage I).[10]

DISCUSSION

Wilms tumor has a propensity to grow rapidly, and children often have massive tumors. The size of the lesion can preclude primary removal, and the clinician must seek alternative forms of treatment. Radiation therapy was one of the early adjuvant treatments employed when operative removal of the tumor was technically difficult.[11,12] The introduction of dactinomycin in 1956 and vincristine sulfate in the 1960s quickly led to their use with and without radiation in children with inoperable Wilms tumor.[3–5,13] Wagget and Koop reported 12 children treated with dactinomycin with or without XRT, or with vincristine alone (2 patients).[4] In all cases, there was a reduction in tumor size, allowing for subsequent nephrectomy. Bracken et al.[5] treated 19 inoperable Wilms tumors with preoperative vincristine, either alone (17 patients) or in combination with dactinomycin for a median duration of 17 days. A marked reduction in tumor size was noted after chemotherapy alone in 16 patients and after additional XRT in another child. Only one tumor remained unable to be resected, and 53% of the patients were alive at last follow-up.

The International Society of Pediatric Oncology (SIOP) has used preoperative treatment for patients with Wilms tumors since the early 1970s.[7] They give all patients preoperative treatment, not just those with tumors unable to be resected. Despite the extensive SIOP experience, there is little specific information regarding the management of patients with tumors considered to be inoperable on initial examination. In North America, preoperative therapy has been used predominantly for patients with Wilms tumors with bilateral disease.[14]

More recently, Dykes et al.[15] reported on 36 children with advanced Wilms tumors treated with preoperative chemotherapy. Nineteen of the 36 had radiographic evidence of metastatic disease at presentation, 12 had intracaval disease, and 5 were judged by radiographic evaluation to have inoperable tumors. All patients underwent biopsies initially and then treated for a median of 13 weeks with dactinomycin, vincristine, and doxorubicin. None received preoperative irradiation. The 75% overall survival for the 36 children at a mean follow-up of 43 months was comparable with that reported in our series. Their impression was that in the majority of cases, the tumors were appreciably reduced in size and the surgical procedure was less difficult after the preoperative treatment.

Ritchey et al. reviewed 30 patients with intravascular tumor extension of nephroblastoma treated with preoperative chemotherapy or XRT.[16] Ten were judged to be inoperable by surgical evaluation, and the remainder were treated based on the radiographic evaluation. There was a major reduction in the size of the tumor and thrombus in most cases. One child had progressive disease before surgery. The 2-year survival was 70% with a median follow-up of 21 months. The conclusion was that preoperative therapy was a desirable alternative to immediate surgery for patients with intracaval extension above the level of the hepatic veins, because of the lessened morbidity.

The review here reported suggests that "inoperability" as a criterion is an adverse prognostic factor independent of stage, because the overall survival of these patients is less than that of children undergoing primary nephrectomies. The growth patterns of these tumors might reflect a different degree of aggressiveness that affects survival, but stage for stage, these patients are not comparable with those reported in other NWTS studies. The stage assigned pretreatment, particularly if the patient does not undergo surgical exploration, is not as accurate as that assigned after complete tumor removal and pathologic examination of the specimen. Patients with stage IV disease probably can be identified reliably, but even for this group of patients, local tumor stage cannot be determined accurately after preoperative therapy. We chose to assign all patients found to have tumors unable to be resected at surgery to stage III. This was based on the assumption that attempts to remove these lesions would lead invariably to a high incidence of residual disease.

A potential factor in the decreased overall survival of the inoperable patients could be undertreatment. Eighty-eight percent of the patients were assigned a pretreatment stage III or IV. However, a preoperative chemotherapeutic regimen of 3 or more drugs was given to only 40% of these patients. During the entire course of treatment, before and after nephrectomy, 16 of these patients received only dactinomycin and vincristine. This would suggest that some patients may have been undertreated, possibly relying on the postresection stage, at which time many patients were "downstaged" (Table 4). Green et al. have pointed out the difficulties in determining the true stage of the tumor after preoperative treatment.[17] This can lead to an underestimation of the inherent aggressiveness of the tumor and can lead to undertreatment. The SIOP trials have shown that postchemotherapy stage inadequately defines the risk of intra-abdominal recurrence in nonirradiated SIOP stage II, node-negative patients.[18]

The clinician should be cautious in staging patients based on imaging studies. Preoperative imaging may suggest extension into the adjacent perirenal fat and invasion of regional lymph nodes, which can then be confirmed at surgical exploration. However, prospective

correlation of pathologic findings to validate the usefulness of computed tomography staging has not been done.[19] Enlarged retroperitoneal benign lymph nodes are common in children and can create significant diagnostic error. Correlation between pathologic findings and lymph node evaluation at surgical exploration in patients with Wilms tumors have found false-positive and false-negative error rates of 18% and 31%, respectively.[20] Current imaging modalities may not have greater accuracy. Liver invasion by right-sided tumors is particularly difficult to assess by computed tomography. Dynamic scanning of the liver after bolus injection is recommended to obtain the best information. Ng et al.[21] noted that most children identified as having probable or possible invasion of the liver on computed tomography later proved to be negative at surgical exploration. Computed tomography did have a 100% predictive value for absence of liver invasion, but deep-seated liver metastases that would not be visible at surgery are uncommon.[22]

Pathologic assessment after preoperative treatment also is fraught with difficulty. International Society of Pediatric Oncology studies have found that histologic patterns could still be recognized after chemotherapy, whereas preoperative XRT caused far more tumor destruction.[23] Central review by the NWTS Pathology Center of the patients reported in this series found extensive post-treatment changes that can preclude accurate classification.[10] However, recognition of anaplastic elements still was possible after preoperative treatment. Four patients in this study with preoperative biopsy diagnoses of favorable histology were found to have anaplasia in the nephrectomy specimen. This was presumably because of initial sampling error.

The role and timing of XRT in the management of inoperable tumors is of great interest; however, the absence of randomization of preoperative irradiation limits the analysis of these patients. Initial review suggested that survival was affected adversely by XRT. However, it appears that the clinicians were selecting some tumors for preoperative XRT after failure of the initial course of chemotherapy. When these patients are excluded from the analyses, there was no difference in survival with the addition of preoperative irradiation.

Regardless of the preoperative treatment modality used, subsequent surgical resection was facilitated by a reduction in tumor size. With the exception of the eight children who died before definitive surgery and one child unable to be included in follow-up, the remaining 122 patients were able to undergo nephrectomies. Evidence that preoperative treatment facilitated nephrectomy is supported by the 19% incidence of surgical complications. This incidence is identical to that for randomized NWTS-3 patients undergoing primary nephrectomies,[2] even though most preoperatively treated children exhibited adverse prognostic variables. These factors include higher tumor stage, intracaval extension, and en bloc resection of other organs, all of which have been shown to significantly increase the risk of surgical morbidity.[2] One would have expected a much higher incidence of complications had primary surgery been carried out in this group of children. However, this decreased surgical morbidity is balanced by an increase in abdominal irradiation and intensive chemotherapy used in these children with their attendant consequences.[17,24]

CONCLUSION

Children with large inoperable tumors selected for preoperative therapy have a worse prognosis than patients who undergo primary nephrectomies. Outcome was particularly poor in patients in whom excision of the tumor could not be carried out. Therefore, nephrectomy was possible in 93% of our patients after preoperative treatment. The approach of preoperative chemotherapy with or without XRT can facilitate subsequent surgical resection in patients with Wilms tumors unable to be resected. However, the determination of "inoperability" probably is best judged at surgical exploration because preoperative treatment can lead to less accurate surgical and pathologic staging. Relying on imaging studies for staging can lead to inaccuracies as well. Preliminary exploration provides an opportunity for surgical staging, and the occasional patient judged to be inoperable by imaging studies may prove amenable to primary surgical removal. This approach will allow treatment plans to be individualized and may avoid undertreatment in these high-risk patients.

With these factors in mind, we would suggest the following algorithm for treatment of patients found with tumors that were unable to be resected or were inoperable. Initial exploration should be performed to assess operability and obtain biopsy of the tumor. Thorough exploration of the abdomen is necessary to detect evidence of extrarenal extension of tumor. If suspicious lymph nodes or other metastatic deposits are found, a biopsy should be performed to document tumor involvement. Patients who are staged by imaging studies alone are at risk for understaging and overstaging. If one chooses to give preoperative therapy based on imaging alone, with or without needle biopsy, the local tumor should be considered stage III and treated accordingly. A consensus recommendation for the duration of the preoperative treatment cannot be determined from this review. Once there is an adequate reduction in the size of the tumor to facilitate nephrectomy, definitive resection should be completed. Serial imaging evaluation is helpful to assess response, but radiographic evidence of persistent disease occasionally can be misleading. Failure of

the tumor to shrink could be caused by predominance of skeletal muscle or benign elements, and a second look procedure to confirm persistent viable tumor may be necessary.[16] Patients who fail to respond can be considered for preoperative irradiation; this may produce enough shrinkage to facilitate nephrectomy. If the tumor remains inoperable, then biopsy of both the primary tumor and accessible metastatic lesions should be performed. Patients with progressive disease have a very poor prognosis, and these patients will require treatment with a different chemotherapeutic regimen. After surgical resection, patients should continue on treatment until they have completed the regimen appropriate for their assigned stage. The need for postoperative XRT was not defined clearly by this review, and the recommendations stated below are the opinions of the authors. All those patients documented by the surgeon or the pathologist to have stage III disease before treatment, including those with stage IV disease and a stage III primary tumor, should undergo XRT. Children with evidence of residual tumor after nephrectomy also need XRT. All patients with stage II, III, and IV disease after preoperative treatment should receive doxorubicin.[18]

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