Wilms' Tumor and Neuroblastoma: Results of Therapy*

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As a result of intensive research during the past 20 years, there is now a more optimistic attitude toward the treatment of children with cancer. Success with new therapies of Wilms' tumor and acute lymphoblastic leukemia have been important factors in generating this new optimism. Despite these and other advances, little success has been achieved in the treatment of children with neuroblastoma. The poor prognosis of these patients is due to the high percentage of widespread disease at the time of diagnosis and lack of effective treatment for advanced disease.

Wilms' tumor and neuroblastoma are numerically among the most common noncerebral malignant solid tumors in children. The purpose of this report is to describe the recent results of therapy.

Incidence of Wilms' Tumor and Neuroblastoma. To provide a perspective of these two diseases, a list of malignant diseases in children under 16 years of age reported to the Medical College of Virginia Tumor Registry between 1964 and 1970 is shown in Table 1. Acute leukemia was the most common malignancy, followed by central nervous system tumors. Wilms' Tumor accounted for 9.7% and neuroblastoma, 6.4% of all the malignancies reported. The importance of these two tumors is considerably increased, however, when we consider only noncerebral solid tumors of childhood; Wilms' tumor accounted for 16% and neuroblastoma, 11% of these tumors.

Wilms' Tumor. Advances in chemotherapy of Wilms' tumor, along with improved treatment modalities in radiotherapy and surgery have increased the survival rate from a 20% two-year survival rate three decades ago to an 80% plus rate within the last 10-year period.

The use of dactinomycin and vincristine accounts for the improvement in chemotherapy. In the early 1950's, nitrogen mustard was tried in the treatment of metastatic Wilms' tumor with little apparent benefit. In 1955, Farber pioneered in the use of dactinomycin in children with or without metastases. This drug has been shown, after extensive trial, to be of considerable benefit in preventing recurrences and in eradicating recurrent and metastatic disease.

Improved radiation treatment has resulted from the development of more sophisticated equipment and from an improved understanding of the natural history of Wilms' tumor. Supervoltage equipment with increased definition has allowed delivery of lower dosages to the tumor, with less radiation scattered into surrounding normal tissue. Additionally, less of the dose is directed to growing bone than with previous orthovoltage equipment when normal bone might absorb as high as 15–20% over that delivered to the tumor.

Improved understanding of the disease includes the observation that the tumor remains localized in its pseudocapsule until the very late stages, allowing the use of localized irradiation of the renal fossa after surgery rather than more widespread treatment. Another observation that lymph node involvement is rare, saves the need for routine irradiation for possible para-aortic node involvement. At the same time, greater understanding of the tumor has

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TABLE 1.

Pediatric Cases of Malignant Diseases Reported to the Medical College of Virginia Tumor Registry, 1964–1970

DISEASES	NUMBER OF CASES	PER CENT
Central Nervous System Tumors		
Optic Glioma	5	2.3%
Astrocytoma	15	6.9
Medulloblastoma	9	4.1
Ependymoma	5	2.3
Craniopharyngioma	3	1.4
Meningioma	1	0.4
Acute Leukemia	48	22.2
Lymphosarcoma	25	11.5
Hodgkin's Disease	9	4.1
Wilms' Tumor	21	9.7
Lymphoepithelioma	7	3.2
Rhabdomyosarcoma	12	5.5
Neuroblastoma	14	6.4
Malignant Schwannoma	3	1.4
Osteogenic Sarcoma	7	3.2
Mixed Mesodermal Tumor	2	0.9
Dysgerminoma	3	1.4
Carcinoma of the Pancreas	1	0.4
Carcinoma of the Maxillary Sinus	4	1.8
Composite Parotid Tumor	1	0.4
Retinoblastoma	4	1.8
Ameloblastoma	3	1.3
Arrhenoblastoma	2	0.9
Ewing's Tumor	2	0.9
Fibrosarcoma	2	0.9
Hemangioendothelioma	2	0.9
Hepatoma and Hepatoblastoma	2	0.9
Osteochondroma	2	0.9
Teratoma	2	0.9
	Total 216	100%

been developed through the efforts of pathologists, with the recognition of a subgroup—the mesoblastic nephroma. This lesion would seem to be of low grade malignancy and may contribute to the well-known better survival in infants.

In the presence of lung metastases, which account for approximately 90% of the cases in which Wilms' tumor metastasizes, it has been observed that low-dose radiation plus chemotherapy can preserve pulmonary function as it cancels disease in at least 60% of such patients. It has also become evident that since two of three patients will have generalized pulmonary involvement, bilateral total pulmonary irradiation is necessary even in the patient with evidence of only one lesion.

According to Tefft, experience has shown that irradiation cannot be relied upon to control liver metastases. Surgical excision is the only sure control of a lesion in the liver if it is solitary or localized to one lobe. When liver irradiation is indicated, a total dose of 3000 rads to the total liver in three weeks time should not be exceeded.

National Wilms' Tumor Study (NWTS). Since the national yearly incidence of Wilms' tumor, estimated to be 500, is too small to permit single institutions and investigators to gain significant information about the treatment of this disease without the investigation being unduly protracted, groups of investigators and institutions combined their efforts in a single investigation so that early answers can be obtained to longstanding questions regarding therapy.

The primary objective of the NWTS, activated in 1969, was to refine methods of treatment. Thus, two specific questions were asked: 1) Is postoperative radiotherapy necessary for treatment of patients with well-encapsulated, localized lesions after what appears to be their total removal? 2) Which of the two chemotherapeutic agents (dactinomycin, vincristine) known to be effective against Wilms' tumor gives the better result and can this result be improved by their combined use?

The secondary objective was to obtain a better understanding of the neoplasm by defining the extent of the lesion at diagnosis (clinical grouping or staging) and relating it to the response to treatment. Five clinical groups (stages) of disease were defined:

Group I—Tumor limited to the kidney and completely resected

Group II—Tumor extends beyond the kidney but is completely resected

Group III—Residual nonhematogenous tumor confined to the abdomen

Group IV—Hematogenous metastases

Group V—Bilateral renal involvement either initially or subsequently

Children were randomized at diagnosis according to their clinical group determined by the surgeon and pathologist. Those in group I were randomized following surgery to receive either dactinomycin alone or dactinomycin plus postoperative irradiation to the tumor bed. Dactinomycin was started and

given in five-day courses (15 μg/kg/d, i.v.) within 48 hours of diagnosis and repeated at 6 weeks, 3, 6, 9, 12 and 15 months, thereafter.

Children in groups II and III, following resection, all received irradiation to the tumor bed. At the same time they were randomized to receive either dactinomycin alone, vincristine alone or the combination. Dactinomycin was administered as outlined for group I patients. Vincristine was given weekly for 7 weeks (1.5 mg/m^2 i.v.) starting at the time of diagnosis, then at 3, 6, 9, 12 and 15 months thereafter, giving two doses four days apart.

Children in group IV received either a preoperative course of vincristine (day 0 and 7) and then had surgery on day 14 or surgery was carried out immediately. Treatment then was identical to that for groups II and III.

Results. It is still too early to draw any definite conclusions from any of the preliminary data. Certain patterns seem to be emerging, however, and are worthy of mention.

Of 208 patients registered, 21 were incorrectly diagnosed. More than half of these cases turned out to be either neuroblastoma or polycystic kidney. Other diagnoses included renal carbuncle, benign teratoma, congenital renal vein thrombosis, hemorrhage into the subrenal gland, hypernephroma and rhabdomyosarcoma. Two cases of mesoblastic nephroma were also registered.

One hundred eighty-seven patients were randomized according to protocol. Patients with clinical group I disease (the lesion limited to the kidney and completely resected) formed the most frequent group and accounted for 83 of these patients. Disease groups II, III and IV were less frequent and contained 47, 39 and 18 patients respectively. The accrual rate by month has shown no seasonal variation in the incidence of the disease.

The mean age at diagnosis for the entire series of 187 patients was 41 months. Group I patients were the youngest (approximately 30 months) and group IV, the oldest (approximately 60 months). The mean ages of groups II and III were approximately equal at 39 months. From the data, it seems clear that with increasing age at diagnosis, the disease is likely to be more advanced.

Approximately 16% of all the patients were black and 48% were females. The right kidney was involved in 46% of the cases. No differences were apparent among the four groups in these parameters.

With regard to the results of therapy, approximately 90% of the patients in clinical group I were free of disease from one to more than 21 months after treatment was instituted. There is no difference in recurrence rate thus far between those who received dactinomycin alone and those who received it in combination with postoperative radiotherapy. If further follow-up substantiates that radiotherapy produces no added benefit in this clinical group, the study will have borne important fruits. The possible untoward late effects of radiation are well known. Disturbances of normal bone growth, radiation nephritis, radiation hepatitis and pulmonary fibrosis are some. Induction of primary tumor by the irradiation of normal structures, while not frequent, is nonetheless a matter of real concern.

Of those with clinical groups II and III involvement, approximately 75% continued in complete remission from one to 21 months after the start of treatment and approximately 60% of these in clinical group IV were similarly free of disease for the same period of time. No differences are apparent thus far between the various treatment regimens in these three groups.

All but one of the metastases or recurrences in relapsed patients developed during the first year of treatment. By far, the most common site of metastases was the lung. Other sites were liver, nodes, bone, spleen and brain. Abdominal recurrences were infrequent. In most instances death was attributed to tumor, but in a few cases no tumor was found and infection was thought to be the cause.

Toxicities to therapy included leukopenia and thrombocytopenia with occasional anemia, nausea and vomiting, radiation dermatitis and hepatitis and alopecia. These were usually reversible.

At the Medical College of Virginia, 11 patients, ranging in age from five months to eight years, have been entered on study (Table 2). Three had clinical group I disease, seven, clinical group II disease, and one, clinical group IV disease. All but one attained complete remission with therapy. Two of the 11 developed metastases at 13 and 16 months following diagnosis and one of them has expired. Eight of the 11 are free of disease from five months to nearly three years after treatment was started. The three oldest patients (3½, 5 and 8 years) in this small series developed recurrences or metastases.

Neuroblastoma. Although there has been marked improvement in survival of children with Wilms' tumor during the last decade, this has not been the case for metastatic and nonmetastatic

TABLE 2.

National Wilms' Tumor Study Medical College of Virginia Patients

CASE	AGE AT DIAGNOSIS	DATE ON STUDY	CLINICAL GROUP	TREATMENT	STATUS
1	19 mos.	4/10/70	I	S, R, Dact	NED
2	10 mos.	6/29/70	I	S, R, Dact	NED
3	23 mos.	2/28/72	I	S, R, Dact	NED
4	5 yrs.	10/29/69	II	S, R, Dact, Vcr	Expired 1/4/71
5	2 yrs.	5/14/70	II	S, R, Dact, Vcr	NED
6	2 yrs.	8/26/70	II	S, R, Dact, Vcr	NED
7	8½ mos.	3/19/71	II	S, R, Vcr	NED
8	1 yr.	7/1/71	II	S, R, Vcr	NED
9	3½ yrs.	10/11/71	II	S, R, Vcr later Dact Adriamycin Cytoxan	Expired 2/5/72 (no response)
10	5 mos.	9/16/72	II	S, R, Vcr	NED
11	8 yrs.	4/6/71	IV	S, R, Dact, Vcr	Recurrence right lung 8/72, later brain

S—Surgery
R—Radiotherapy
Dact—Dactinomycin
Vcr—Vincristine
NED—No evidence of disease

neuroblastoma for the same time period, primarily due to the diffculty in early diagnosis and lack of effective treatment for advanced disease. Chemotherapy, in contrast to Wilms' tumor, has not been very successful. An overall cure rate of 35–40% has been reported. In patients under one year of age who have localized disease, survival rates as high as 68–70% have been achieved; however, in generalized disease the survival rate has been estimated at about 12%.

Between 1957 and 1968, 21 children with neuroblastoma and two children with ganglioneuroblastoma were treated at the Medical College of Virginia. Of the entire group, only two patients are alive; one child with intrathoracic neuroblastoma, age five months at diagnosis, has no evidence of disease after resection and postoperative radiotherapy. Another, age 6 months at diagnosis with widespread disease, has been free of disease for four years, after one year of treatment with cyclophosphamide and vincristine. Six of the patients were under one year of age, and 14 were two years or older at diagnosis.

The commonest site of the primary tumor was the adrenal gland (52%). Other less common sites included the retroperitoneum (17%), posterior mediastinum (17%) and the brain (4%).

In the majority of cases (74%), the disease was already widespread at the time of initial examination. Distent metastases occurred most often in bones (48%), bone marrow (48%), and liver (48%), although at autopsy an unusually high percentage (35%) had metastases to the lungs and pleura. Those with regional disease developed metastases within 12 months of diagnosis. Only three children, all with regional disease, had complete resection of tumor. All others had either partial resection or biopsy.

Four children died before any treatment could be instituted. Fifteen of 23 received postoperative radiotherapy. A variety of chemotherapeutic agents including vincristine and cyclophosphamide were included as part of the initial treatment program in 15 patients with distent metastases and in four with regional disease.

The median survival time for the entire group was six months, with the longest survivor still alive at seven years. Those with the primary site located in the adrenal gland had the shortest median survival time (4 months).

Sawitsky and Desposito (3) have reported their results using either cyclic or sequential vincristine and cyclophosphamide in high or low dosage for treatment of generalized neuroblastoma. Their results also do not bear out the early enthusiasm shown for these agents for treatment of neuroblastoma. Of 47

TABLE 3

Staging of Neuroblastoma

STAGE I:	Tumor confined to the organ or structure of origin.
STAGE II:	Tumors extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the homolateral side may be involved.
STAGE III:	Tumors extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.
STAGE IV:	Remote disease involving skeleton, organs, soft tissue, distant lymph node groups, etc. (See IV-S.)
STAGE IV-S:	Patients who would otherwise be Stage I or II, but who have remote disease confined only to one or more of the following sites: liver, skin or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).

patients treated, only two are alive for more than 24 months with no evidence of disease. The median survival in the whole group was 37 weeks. If a response occurred, median survival was prolonged to 65 weeks.

Other drugs used have also produced disappointing results and include 6-mercaptopurine, prednisone, methotrexate, dactinomycin, daunorubicin, and nitrogen mustard. Newer agents such as adriamycin and ifosphamide are currently under investigation.

Although results of treatment continue to be poor, advances have been made in the understanding of the disease process. A new staging system has been developed based on certain patterns of origin and clinical behavior found to affect prognosis, which takes into account the peculiarities unique for neuroblastoma (Table 3) (1). Data based on this system indicates that: 1) Patients with stage IV-S have a better prognosis than those with stage IV disease; 2) The proportion of patients in stages III and IV increases with age; 3) The presence of bone metastases, to be distinguished from bone marrow involvement with positive x-ray findings, almost always heralds a fatal outcome; and 4) Data confirm the well-known better survival of patients under one year of age.

A second potential contribution has been the development of a simple, reliable "dip-stick" test for detecting the early presence of neuroblastoma (2). The test is based on the fact that up to 80% of the children with this disease excrete excess catecholamine or one of its metabolites, 3-methoxy-4-hydroxy-mandelic acid (VMA) in the urine. Strips of chromatography paper impregnated with paranitroaniline, sodium nitrate, and anhydrous potassium carbonate are dipped into a urine sample or just pressed against a wet diaper. Within ten minutes, the color of the paper changes to orange or purple if either VMA or normetanephrine is present in urine. The test may be used by private practicing physicians for routine screening on all children under five years of age. If used at regular yearly intervals, it is conceivable that a significant impact upon survival of neuroblastoma may be achieved by early diagnosis before metastasis has occurred.

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