Survival Determinants in Patients with Nephroblastoma (Wilms' Tumor)

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Nephroblastoma is the only renal neoplasm seen with frequency in childhood[1] and has an incidence of approximately 7.8/million children/year in the United States; and a relatively similar incidence worldwide. The median patient age at discovery of this tumor is three years. The diagnosis is rarely made after the age of seven.

Chromosomal and biochemical studies suggest that there is an uncommon "heritable" form and a much more common "non-heritable" form of Wilms' tumor.[2,3] In the former, the neoplasm develops at a younger age and is more frequently bilateral and multicentric than in the "non-heritable" form. The chance of offspring developing Wilms' tumor in the heritable group is approximately 30% vs. <2% in the non-heritable form with unilateral disease.[4,5]

A group of congenital anomalies are associated with the occurrence of Wilms' tumor, but are found in a relatively small percentage of these children.[6] Hemihypertrophy (asymmetrical enlargement) occurs in 2.9% and aniridia in 1.1% of these children, neither condition having a known effect on long-range survival. Patients with Wilms' tumor and aniridia frequently have a gene defect, an identifiable 11p13 chromosomal deletion.

Clinical Presentation and Diagnosis

Children with nephroblastoma are usually identified initially because of the discovery of an abdominal, usually subcostal, mass. Gross hematuria, hypertension, recognized weight loss, or significant fever occur in less than 10%.

The major differential diagnostic possibilities in such patients include neuroblastoma and forms of benign renal disease. Ultrasonography will demonstrate that the mass is solid or cystic, excretory urograms establish its connection with the kidney, computerized tomography delineates its extent and MRI elucidates the possible involvement of adjacent structures or nodes. Venography may identify extension into the inferior vena cava through the renal veins, and angiography is used in children with bilateral masses to facilitate attempts to preserve renal tissue on both sides when bilateral tumors are found. The diagnosis is routinely confirmed by nephrectomy without prior biopsy.

Significance of Specific Pathologic Features

By approximately 1976, a perplexing situation had developed in the management of Wilms' tumor in the U.S. At this time, if one accepted the results of the most favorable arm in all of the randomized trials of the National Wilms' Tumor Study (NWTS), the overall survival rate among patients with Wilms' tumor was approximately 90% with the patients on relatively non-intensive chemotherapy regiments. Attempting to improve upon this result with more intensive regimens would place 90% of the patients at risk from increased toxicity, not previously a significant problem in the NWTS. Thus, increasing the intensity of therapy might have deleterious overall effects. This quandary was resolved when Beckwith and Palmer, following analysis of 427 specimens from the NWTS, found that they could "blindly" identify a group consisting of approximately 11% of the total patients in the study whose presence contributed over 52% of the mortality.[7] This observation has been confirmed in subsequent NWTS trials and has resulted in worldwide acceptance of the concept that there are two broad histologic categories, i.e., favorable and unfavorable (as well as several subcategories of the latter), and that these two major categories are of paramount prognostic significance. The 11% with unfavorable histologic features have been divided into three subcategories: anaplastic, clear cell, and rhabdoid tumors. Patients with anaplastic tumors, except when disseminated at diagnosis, have survival rates only slightly lower than those of patients in the favorable category. The clear cell sarcomas of kidney metastasize more commonly than favorable forms, particularly to osseous structures. Rhabdoid tumors have the lowest survival rates. It is debatable whether the latter two tumors should be included under the "umbrella" of the term Wilms' tumor.

Staging

A staging system based both on extent of disease and the initial surgical procedure performed, was developed by the NWTS.[8] The distinction between favorable and unfavorable histology was incorporated into the system for assigning therapy regimens in the third NWTS. Otherwise the classification (Table I) has been altered relatively little during

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the 20-year course of this group's activity. The histologic distinctions recognized by Beckwith and Palmer can be correlated with stage of disease, i.e., in NWTS-2, 2/3 of the patients with favorable histologic patterns had early stage lesions, whereas 50% of those with unfavorable histologic patterns had an advanced stage at diagnosis.

Table 1

Definitions of Stages* in the National Wilms' Tumor Study

I. Tumor limited to kidney and completely excised.

The surface of the renal capsule is intact. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of resection.

II. Tumor extends beyond the kidney but is completely excised.

There is regional extension of the tumor, i.e., penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. The tumor may have been biopsied or there has been local spillage of tumor confined to the flank. There is no residual tumor apparent at or beyond the margins of excision.

III. Residual non-hematogenous tumor confined to abdomen.

Any one or more of the following occur:

a. Lymph nodes on biopsy are found to be involved in the hilus, the peri-aortic chains, or beyond.

b. There has been diffuse peritoneal contamination by tumor such as by spillage of tumor beyond the flank before or during surgery; or by tumor growth that has penetrated through the peritoneal surface.

c. Implants are found on the peritoneal surfaces.

d. The tumor extends beyond the surgical margins either microscopically or grossly.

e. The tumor is not completely resectable because of local infiltration into vital structures.

IV. Hematogenous metastases.

Deposits beyond Stage III; e.g., lung, liver, bone, and brain.

V. Bilateral renal involvement at diagnosis.

*Staging, which is on the basis of gross and microscopic tumor distribution, is the same for tumors with favorable or unfavorable histologic features. The patient should be characterized, however, by a statement of both criteria; e.g., Stage II, favorable histology or Stage III, unfavorable histology.

The major determinants of outcome are: (a) the presence of favorable or unfavorable histologic features; (b) evidence of hematogenous metastasis; and (c) lymph node involvement. Relatively *minor* factors in determining prognosis include extension through the lumen of the renal vein to the *vena cava,* intraoperative tumor "rupture," direct abdominal extension of the tumor to adjacent organs, tumor weight, and patients age.[9] The length of this list of factors which do *not* independently influence outcome, reflects the extreme sensitivity of this tumor to chemotherapeutic agents, even when locally invasive or disseminated.

Therapy

The marked responsiveness of nephroblastoma to chemotherapy is almost unique among adult or childhood tumors. During the early history of its therapy, a five-day course of a single agent (actinomycin-D) made a major difference in outcome. Further, such responses have proved to be remarkably durable. Two-agent therapy with actinomycin-D and vincristine was demonstrated to be most effective by 1976, and subsequently, all therapy regimens included both agents. These two agents have remained the sole therapy, following surgery, for favorable-histology, limited-stage disease.

Therapy is now sharply divided between the two major histology-determined groups. The favorable group have received progressively shorter courses of chemotherapy, and reduced or absent radiotherapy. Survival rates continued to be >90% on these short and non-intensive therapy regimens. Patients in the unfavorable category have been placed on more intensive and longer chemotherapy regimens with continued use of local irradiation. The results in this minority group have been mixed, with decided improvement in some categories and little change in others.

The addition of Adriamycin to the basic regimen has resulted in minor improvement in the therapy of some categories of advanced disease (only) and the addition of cyclophosphamide has apparent usefulness in the management of clear cell and advanced stage anaplastic forms. Neither agent is now used in the management of a large majority of patients with Wilms' tumor.

There has been progressive decrease in the use of radiotherapy and of its dosage when used. At the present time, most patients with favorable histology Stage I or II disease receive no radiotherapy and patients with favorable histology in Stage III receive relatively low-dose therapy.

Survival rates in the group with favorable histology (NWTS) have been so high that in NWTS-4, the study now in progress, one of the principal questions posed in the randomized trial is a socio-economic one. It concerns whether a one-day continuous infusion of actinomycin-D can replace the five-day infusion regimen by which this drug has been traditionally administered, and thus reduce costs, inconvenience, and family stress.

The approach to metastatic or recurrent disease in the case of nephroblastoma is more aggressive than in most other tumors and this has been justified by favorable outcome. Historically, a majority of the patients treated with a single course of actinomycin-D, who had subsequent pulmonary metastasis, were "salvaged" by additional courses of actinomycin-D. With the exception of those patients with osseous metastases, or widespread abdominal involvement, both of which are uncommon, the results of salvage therapy following relapse are relatively good. Approximately 50% of these patients enter the group of long-range survivors. These results are the products of combinations of surgery, radiotherapy, and chemotherapy, with or without the addition of additional chemotherapeutic agents.

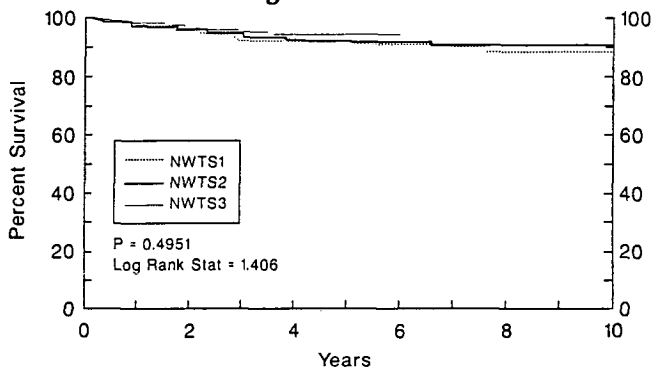
Survival

The survival experience in NWTS-1-3 for patients in Stages I-IV with favorable histology is illustrated in Figures 1-4. The influence of unfavorable histology is shown in Table 2 which provides survival data on each of the small histologic subtypes of this category when treated by two therapy regimens of NWTS-3.[9]

The European experience with Wilms' tumor is best illustrated by the results of the studies carried out by the International Society of Pediatric Oncology (SIOP) which includes major European centers.[10 11 12] These trials have concentrated on the question of the efficacy of presurgical therapy, i.e., irradiation, chemotherapy, or both, before as well as after operation. During the course of their trials, survival rates have been steadily increasing (Figure 5). The advantages of presurgical therapy have not been generally appreciated in North America; but it is apparent that the results of both forms of management in major institutions result in almost equally high rates of survival.

Figure 1

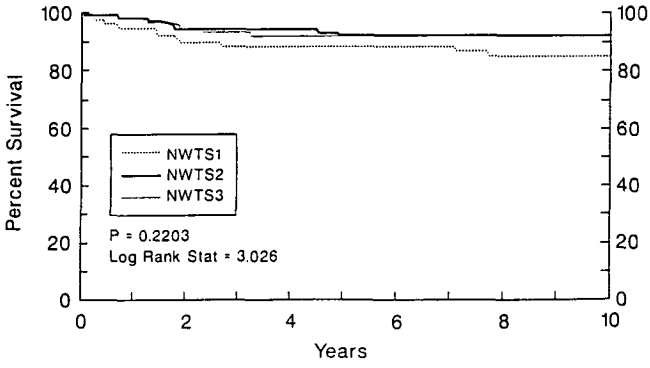
Stage I: Survival



Survival curves of patients in Stage I with favorable histology from NWTS-1, 2, and 3. The total number of patients located for information relative to survival in NWTS-1 (1968-1974) (all stages) was 389 at onset, 336 at two years, 312 at four years, 295 at six years, 260 at eight years, and 151 at 10 years. The comparable figures for NWTS-2 (1974-1980) were 650 at onset, 564 at two years, 457 at four years, 314 at six years, and 132 at eight years. The comparable figures for NWTS-3 (1980-1985) were 972 at onset, 693 at two years, and 267 at four years.

Figure 2

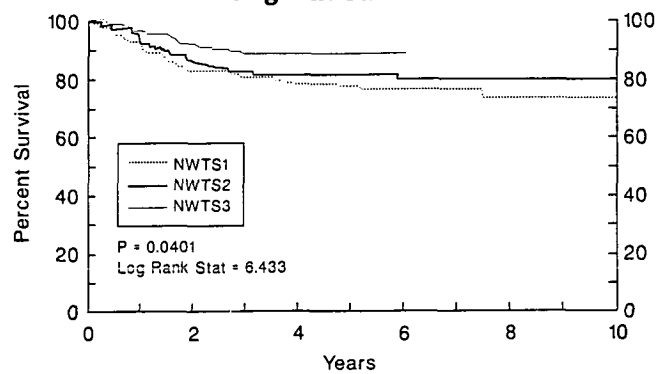
Stage II: Survival



Survival curves of patients in Stage II with favorable histology for NWTS-1, 2, and 3. (See caption for Figure 1.)

Figure 3

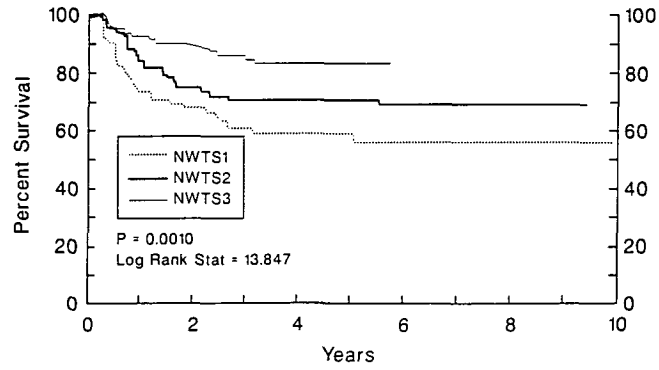
Stage III: Survival



Survival curves of patients in Stage III with favorable histology for NWTS-1, 2, and 3. (See caption for Figure 1.)

Figure 4

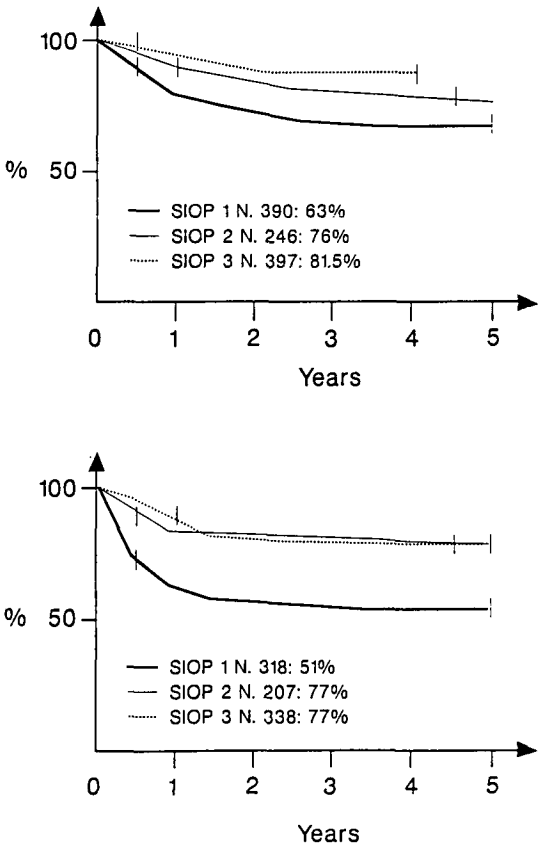
Stage IV: Survival



Survival curves of patients in Stage IV with favorable histology for NWTS-1, 2, and 3. (See caption for Figure 1.)

(Figures 1-4 provided by Dr. Nathan Kobrinsky and the NWTS Committee)

Figure 5



Actuarial survival curves (top) and disease-free survival curves (bottom) in studies carried out by the International Society of Pediatric Oncology (SIOP) with 390 patients entered in the first study (1971-1974); 246 in the second study (1974-1976); and 397 in the fifth study (1977-1980). The survival curves include patients in all stages. The recurrence-free survival curves do not include patients in Stage IV at diagnosis.

Survival rates in most developed countries are progressively increasing to reach levels of approximately 90%,[13] where they "plateau;" whereas in Third World Countries, the survival rates are significantly lower.[14] Some major cancer centers attract patients in advanced stages or with otherwise complex problems, and this is reflected in lower survival rates.

Tumor recurrence occurring more than two years following the end of therapy is uncommon. The therapy of late pulmonary recurrence is reasonably effective and a survival rate of greater than 50% is expected. Abdominal relapse is less common and survival rates, lower. In addition to the influence of Stage and histology on the relapse rate, a number of local relapses have been associated with failure to follow the details of radiotherapy guidelines.[15] [16] Death from Wilms' tumor more than five years following the end of therapy is a reportable occurrence.

Second Malignant Neoplams and Other Long-Term Adverse Events

A "follow-up" study of 2,438 patients enrolled in NWTS-1-3 between October, 1969 and December, 1982, identified the occurrence of 15 second malignant neoplasms (SMN).[17] According to U.S. incidence rates for 1973-1977, the expected rate of new neoplasms in this group would be 1.77, resulting in a relative risk of 8.5 with a 95% confidence interval (CI) of 4.7-14.0. The cumulative risk of SMN at 10 years was 1%. Among those patients who received irradiation in their initial treatment, the relative risk compared to standard rates were 12/1.11 = 10.8 (95% CI = 5.6-18.9), and for those who did not receive irradiation, 3/0.60 = 5.0 (95% CI = 1.0-14.6). Among the 15 patients in whom SMN occurred, the original disease process was bilateral in four and multicentric in one. Seven of the 15 patients who developed SMN died from 0.2 to 0.9 years from the time of diagnosis of the SMN. Eight are alive, including four greater than four years and three greater than five years since the appearance of the SMN.

Table 2

Wilms' Tumor: The Unfavorable Histologic Forms in the NWTS
Relapse-Free Survival and Survival by Histologic Subtype with Two Treatment Regimens

Histology*	Stage**	Therapy Regimen**	# Patients Evaluated	% Relapse-Free		% Alive	
				2 Yrs.	4 Yrs.	2 Yrs.	4 Yrs.
Anaplastic	I	DD-RT	10	80.0	80.0	77.8	77.8
		J	5	100.0	100.0	100.0	100.0
Anaplastic	II-IV	DD-RT	21	36.7	36.7	43.6	37.4
		J	12	82.5	82.5	81.8	81.8
Clear cell sarcoma	All	DD-RT	25	75.3	70.6	87.8	74.8
		J	25	73.9	60.3	95.7	76.1
Rhabdoid sarcoma	All	DD-RT	13	23.1	23.1	33.8	25.4
		J	18	26.7	26.7	25.9	25.9

* According to Central Pathology (NWTS)
** Final Stage and regimen reported by the institution

Condensed table from D'Angio, *et al*, Cancer (in press) (Reference #9)

Among the 15 patients with SMN in the NWTS, 12 had received irradiation which was, in almost all instances, of a higher dosage than would have been administered in subsequent NWTS studies. In addition to actinomycin-D and vincristine, four of them had received Adriamycin, a drug employed only in advanced disease. Eight of the 15 patients with SMN were in Stage III at diagnosis whereas the incidence of Stage III in the total study population is <25%. In 13 of these 15 patients, the SMN occurred within seven years of the initial registration in the NWTS.

Data regarding SMN for decades after the first 10 years post-diagnosis are less complete. The Late-Effects Study Group, an international body representing large pediatric centers, initially reported a 3.3% instance of SMN at a point 20 years following diagnosis for *all* childhood cancer survivors.[18] In a more recent report, there was an 8.5% instance of SMN at the 20 year point among children in this study who survived two years following diagnosis. However, most of the patients in this international study received more irradiation and more intensive chemotherapy than is included in either past or current Wilms' Tumor protocols.[19] Some studies suggest that familial cancer predisposition may be a major factor among patients in which SMN occurs.

Relatively acute toxic effects of therapy—cardiac, hepatic, or renal—occur in a small percent of the larger series of patients treated for Wilms' tumor. As far as can be determined, these are almost always self-limited and identified (and alleviated) during the first decade following therapy. Some musculoskeletal deformity, secondary to irradiation, is seen among Wilms' tumor survivors, particularly those treated with orthovoltage prior to 1975.[20] These have not been associated with letahal complications. Several patients with late recognition of cardiomyopathy secondary to anthrocycline therapy have been reported.[21] This would be of concern only in those patients in advanced stages of nephroblastoma in which Adriamycin was administered.

Several studies have suggested that late renal disease may result from early nephrectomy *per se*,[22] but this has not been seen in the NWTS or other large series.[23]

Summary

The responsiveness of nephroblastoma to chemotherapeutic agents has resulted in a>90% long-range survival in developed countries worldwide. Among groups of patients with localized disease and favorable histologic features, survival rates are significantly higher than this. The incidence of relapse more than five years following the end of therapy is <1%, and after 10 years, almost unknown.

Second malignancy occurs with approximately 8.5 times the frequency of rates in the general population although, only 1% of the total group of survivors are affected. Its occurrence is concentrated among those patient groups with unfavorable histology and advanced-stage disease who have received the most intensive therapy, both irradiation and chemotherapy. It primarily occurs during the initial eight years of surveillance. Other long-range untoward effects of therapy are uncommon and can be recognized in childhood.

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