Treatment of the Wilms' Tumor with Actinomycin D

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One of the most common malignant retroperitoneal tumors of childhood is nephroblastoma or Wilms' tumor which was described by Gairdner[1] in 1828, and in detail by Max Wilms in 1899.[2] This tumor is seldom seen after childhood and rarely effects both kidneys. The ratios between the right and left kidney, and boys and girls are equal in most of the series reported.

The tumor itself is thought to be embrionic in origin and to consist of mesodermal abortive embryonic renal elements as well as atypical supporting connective tissues. It grows within the kidney and spreads by invasion of the renal capsule directly to neighboring tissues and organs via the lymphatics to regional lymph glands, and most commonly to the lungs, or, occasionally through the blood to the extrapulmonary organs. In some cases implantation metastases to the urinary collecting system can occur, and if the renal capsule tears off spontaneously or accidentally, seeding within the peritoneal cavity may follow.[3-8]

Common findings are a mass in the abdomen, pain, hematuria and sometimes anemia and fever. Clinically about 20-50 per cent of the cases show distant metastases at the first examination,[3 7-9] and about 95 per cent of Wilms' tumors can be diagnosed clinically before operation with the aid of pyelographic x-ray studies.

Treatment

Either radiotherapy or surgery was used for the treatment of Wilms' tumor in the past, but without great success.[5 10-22] A combination of

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these methods were used between 1940 and 1947 by Gross and Neuhauser,[23] and two year survival in this series was 32.2 per cent with surgery alone and 43.3 per cent with surgical exicision of the the tumor plus immediate irradiation. In the course of time combined the approach became common practice in most therapy centers because of higher survival rates.

To achieve even better figures some modifications of the combination technique were tested. There are some advocates of preoperative irradiation followed by nephrectomy and post operative irradiation,[13 17 24 25] some prefer nephrectomy and irradiation only after surgery [7 23 26] and others use preoperative irradiation and nephrectomy.[14 16 27 28] Klapproth[21] reviewed the literature between 1940 and 1958 and found no significant difference among the results of treatment with these modifications.

Some chemotherapeutic agents have been tested on Wilms' tumor since their introduction into the clinical treatment of cancer. Among these alkylating agents and their derivates,[29-31] antifolic acid,[32] Mytomycine,[30] and, the most widely used and the most promising, Actinomycin D have been tried.[30 32 36 35] With this agent potentiation of the x-ray effect was also reported.[36 38 39-45] Later on Vincristine was also found to be effective against Wilms' tumor.[33-35]

In 1960 Farber and D'Angio[37] published the clinical results of Actinomycin D combination with nephrectomy radiotherapy treatment, which seemed to give higher changes of a cure than the others, and later D'Angio[40] also reported a 37 per cent survival in 15 metastatic Wilms' tumors treated with a combination of Actinomycin D and x-ray irradiation, a figure which had never been achieved by any other method.

Prognosis and Criteria For Survival

The prognosis of Wilms' disease depends upon many factors. Therapeutic modalities, the size of the tumor, the degree of spread, cell differentiation and, maybe to a lesser degree, other signs and symptoms, can all affect the issue. Because the disease is not very common, and a large series cannot be collected to give significant statistical evidence in terms of these factors, their prognostic evidence is sometimes difficult to interpret. There are some, however, which most authors believe can affect the prognosis, and many believe that the age of the patient plays an important role.[5 13 19 20 23 24]

Lattimer[7] reports a 73.3 per cent three-year survival for patients less than two years old, and 90 per cent for those operated upon before

the age of one year, while only 18.5 of the children older than two years lived three or more years. However, it must also be remembered that the number of Wilms patients under two years of age who are seen by physicians is only about 13.4 per cent of their total.

Gross and Neuhauser[23] believe that the degree of cell differentiation does not play an important role in prognosis, and some regard hematuria as a poor prognostic sign. Collins[3 9] postulated that the time patient risks recurrence of Wilms' tumor is his age at the time of diagnosis plus the 9 months' gestation period. If the patient lives longer than that without any recurrence the disease can be considered cured. Others believe that a two year period without recurrence after the treatment gives a fair chance for cure.[7 21 23] Klapproth's[21] review shows that in 478 cases 84 per cent of the patients died of the disease within the first year, and 10 per cent within the second year after treatment.

Treatment Policy

In our department we treat Wilms' cases routinely as follows. For primary tumors we give 3000 rads total tumor dose (150 rads daily) at the midplane of the tumor bed by using alternate daily anterior and posterior skin ports which include vertebral bodies. (In a few cases treated between 1957–1961 the minimum 2500 rads tumor dose were given.) If the tumor capsule is found to be broken during the operation we irradiate the whole abdomen with the same tumor dose with protection of the normal kidney.

For secondary deposits, usually seen in the lungs, our irradiation ports cover the total lung field, with lead protection on the scapulas and spinal cord, and we give a total of 1250 rads at midplane of the lungs. Even in a single blood-borne metastasis we irradiate the whole lungs. In some large secondary deposits which did not disappear after the total dose was given, an additional 500 rads with modification of the part of treatment port was added to the tumor dose. If this large focus still persisted or appeared to be a regrowth, the case was referred for surgical excision. For extrapulmonary metastasis we irradiate the secondaries with a minimum of 3000 rads tumor dose.

For our Actinomycin D - combined cases we give a 100–200 mcg. i.v. dose daily, or every other day, and complete it to a total of 60 mcg. per kg body weight. We give only one course of treatment, with each daily dose injected just before x-ray treatment.

The following physical factors are used: 240 k W, 15 mA, 50 cm T.S.D., Th filtration (0,4 Sn, 0,25 Cu, 1Al), H.V.L. being 2.7 mm Cu.

Material and Results

Between March 1957 and March 1966, 39 cases of Wilms' tumor were referred for x-ray treatment, and in this group a survival of at least three years was found to be possible. Our total series consisted of three groups of patients: the first was treated with nephrectomy and radio-therapy, the second with nephrectomy, radiotherapy and Actinomycin D, and the third came for treatment with distant metastases plus primary tumor on first examination. The results for the first two groups are given in Table I.

TABLE I

RESULTS FOR THE FIRST TWO GROUPS

Type of treatment	Nephrectomy Radiotherapy	Nephrectomy Radiotherapy Actinomycin D
No. of patients	16	15
Living without disease	3	8
Died of disease	8	3
Retreated for metastases	5	4

All the patients with the Actinomycin D - combination were treated after 1962, when the drug became available for use in Turkey.

Primary tumors were removed seven cases out of the eight which were referred to us for treatment for distant metastases and one was inoperable. Metastases were found in the lungs in seven cases and in the bone in one, and all the patients were treated with the Actinomycin D-combination. Table II shows the results of this group and these of the other cases where metastases developed during the follow-up period, and which were treated again with the technique described above.

TABLE II

RESULTS IN METASTATIC WILMS' PATIENTS

	Metastases seen on first examination.	Metastases seen and retreated during follow-up period.
No. of patients	8	9
Treated with Actinomycin D	8	7
Treated without Actinomycin D	0	2
Living without disease	0	4
Died of disease	8	3 *
Died of other causes	0	2

* Including two cases treated without Actinomycin D.

Of nine cases where metastases developed during the follow-up period after the first treatment, eight were seen in the lungs and one was found in the medulla spinalis and checked by biopsy. In all these cases metastases appeared between three and 18 months after treatment, and survival was at least three years after the last metastatic focus disappeared. The two patients in this group treated without Actinomycin D soon died and we therefore abandoned this method. Of the two other deaths from unrelated causes, one was from bronchial pneumonia which occurred six years after the last evidence of single metastases had disappeared by obligatory pneumonectomy. The other patient died in a traffic accident apparently free of disease, four months after the last treatment.

Discussion

The results of the treatment of Wilms' tumor with and without Actinomycin D can be seen in Table I, which shows the superiority of the Actinomycin D combination over routine nephrectomy and radiotherapy treatment. The average age of all the patients was four years, two in the group treated by nephrectomy and radiotherapy and three in the Actinomycin D combined group being under two years old. None of them were under one year old, and hematuria was seen in equal numbers of patients in both groups. It is thus apparent that age and hematuria cannot be considered to have influenced our results. Other clinical, laboratory and pathological data suspected of affecting the prognosis were not found to be significant in our series. We feel, however, that these factors must be studied in a larger series, and hope to present further results in the future.

As was indicated in relatively recent literature,[37-45] Actinomycin D and irradiation increase the chances of survival with Wilms' tumor; this was further stressed, predominantly in the older age group, by our control series, in whom the two year survival which was found to be 18.5 by Lattimer,[7] was similar, though they were only treated by nephrectomy and irradiation.

In Table II one can follow the results of treatment of metastatic Wilms' tumors. If the metastases were already developed on first examination the prognosis is hopeless, even with vigorous treatment, and we lost all eight of our patients in this group. It is interesting to note that the presenec of distant metastases is not an indication of inoperability. Some of the patients in this group died from toxicity and intervening infections interpreted as the results of treatment, while others died from recurrence

of the metastases of which similar experiences have previously been reported in the literature.[37 38 41 42]

We now plan to use repeated courses of Actinomycin D or Vincristine during the follow-up period in this type of case. If, on the other hand, metastases develops during the follow-up period after the first treatment and is treated again with irradiation and Actinomycin D, the prognosis seems to be much better. Of the seven out of nine patients in this group who were so treated, four survived at least three years after the last treatment without any evidence of recurrence. Of these metastases, one appeared within the medullary canal causing paraplegia and the other three were in the lungs - two multiple and one single.

Our experience indicates that distant metastases must be vigorously treated in combination with Actinomycin D. The size, location and distribution of the metastases in the lungs does not seem to play a role in the prognosis. A total of 1,250-1,500 rads, combined with Actinomycin D, can eradicate the tumor. In cases of metastatic Wilms' tumors our results were similar to d'Angio's,[40] and we believe that this type of therapy still remains the best method for the control of distant metastases.

Summary

A review of the literature concerning Wilms' tumor is presented, followed by a description of various treatments for the disease, concluding that Actinomycin D with x-ray irradiation has proved the most successful to date.

Thirty-nine patients with Wilms' tumor, some of whom also showed distant metastases, were treated at Hacettepe Hospital between 1957 and 1966, by nephrectomy and radiotherapy, or nephrectomy, radiotherapy and Actinomycin D (which became available in Turkey after 1962). The latter treatment was found to be far supperior to former.

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