The Management of Wilms' Tumour*

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SUMMARY

This report is based essentially on 45 patients with Wilms' tumour treated during the period 1951 - 1967 with comments on a modified régime in 20 patients treated since 1968.

During the period 1951 - 1967 the standard treatment was nephrectomy and radiotherapy; cytoxics were added from 1959. The over-all long-term survival was 42%, but all infants under the age of 1 year have survived. Cytoxics increased the over-all survival rate from 19% to 55%. Although we aimed at giving postoperative irradiation only, 10 patients received pre-operative therapy because of the enormous size of their tumours and/or malnutrition. Eight of these patients have survived.

In view of the above, all patients, excepting infants under 1 year, have received pre- and postoperative X-ray therapy since 1968. We have also modified the cytoxic régime and all patients have been given repeated courses of actinomycin D, while those with metastases or recurrence have also received vincristine. The over-all survival rate to date is 60%.

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In the period 1951 - 1970 the Childhood Tumour Clinic of the University of Cape Town dealt with 808 cases of malignant disease in childhood. Of these patients, 79 children (9·7%) suffered from Wilms' tumours which form the basis of this discussion.

In the management of Wilms' tumours, as indeed in that of any childhood neoplasm, the first step is to ensure minimal handling of the tumour to avoid unnecessary dislodgement of malignant cells into the circulation. Special investigations should be restricted and in most cases limited to X-ray of the chest, intravenous pyelography and possibly arteriography.

The standard treatment for Wilms' tumour today consists of a combination of surgery, radiotherapy and chemotherapy, although in infants under the age of 1 year, one or both of the latter modalities may be omitted. Of the 79 cases in our series 14 arrived in a terminal state due to metastases, malnutrition or intercurrent disease. They died within a few days of admission and will not be considered. Twenty have been treated since 1967 and because the follow-up is less than 3 years these cases are not included in the detailed analysis of the results of treatment. This article, therefore, deals essentially with the methods and results of treatment in 45 cases adequately treated during the period 1951 - 1967. However, since 1968 we have modified our treatment and therefore a few remarks on the methods used and results obtained in the last 20 cases may be of interest.

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SURGERY

Surgery is essential, although there are records of a few cases with bilateral tumours who have survived without removal of the second kidney. The operation which aims at early ligation of the pedicle and dissection of the neighbouring glands, is best performed by the transperitoneal approach. This is particularly important when there has been extension into the inferior vena cava. Surgery also plays a role in the treatment of isolated secondaries, e.g. solitary pulmonary metastases, and one of our patients in whom such a metastasis was excised is still alive and well 4 years later.

RADIOTHERAPY

Radiotherapy is also regarded as essential by most workers, although there is now a strong body of opinion in favour of withholding radiotherapy in infants under the age of 1 year and it has been proposed that radiotherapy can be omitted in Stage I tumours in older children. Be that as it may, we have used radiotherapy in a total dosage of up to 3 000 rads (depending on age) spread over 3 - 4 weeks, whenever possible. In most of the 45 patients it was given postoperatively only, commencing 3 - 4 days after the operation.

The value of pre-operative irradiation remains a controversial issue and there are many who condemn it outright. This used to be our viewpoint but because of the large size and fixity of some tumours and the poor nutritional state of many of our patients, we have been forced to resort to pre-operative therapy (up to a dose of 1 200 rads) in about 25% of cases. The results have been most significant, especially when correlated with the ages of the patients (Table I). With the use of pre-operative radiotherapy the over-all long-term survival was 80% as compared with 31% when only postoperative irradiation was given. This was indeed a surprising finding because the children who received pre-operative irradiation were poorer risks, with larger tumours. It should also be noted that the improved results were obtained in children over the age of 1 year. There is little doubt that in the type of patient seen by us and in our hands, pre-operative therapy has improved the results in children over the age of 12 months and particularly in those over 3 years. It certainly renders the surgery much easier and lessens the risks of local recurrence and of rupture of the tumour during manipulation. Since 1968 we have, therefore, used pre-operative radiotherapy in all children over 1 year old. It has to be conceded that this method of treatment demands absolute accuracy of diagnosis and for this reason we have had to perform arteriography in many of the

TABLE I. RADIOTHERAPY

	Postoperative DXR only			Pre- and postoperative DXR		
	No. of cases	Survivors	Survival rate	No. of cases	Survivors	Survival rate
Less than 1 year	**2**	**2**	**100%**	**1**	**1**	**100%**
12 - 35 months	**17**	**7**	**41%**	**3**	**3**	**100%**
More than 3 years	**16**	**2**	**13%**	**6**	**4**	**67%**
Totals	**35**	**11**	**31%**	**10**	**8**	**80%**

patients. The arteriograms have proved to be of inestimable value, not only in confirming the diagnosis, but also in excluding the presence of a second tumour in the other kidney.

Radiotherapy is also of some value in the treatment of multiple pulmonary metastases and we have used it in a dosage of 1 250 rads with favourable, although temporary, results.

CYTOTOXICS

Cytotoxics have now become almost a *sine qua non* in the treatment of Wilms' tumour. We have used cytotoxics since 1959—nitrogen mustard from 1959 to 1962 and actinomycin D from 1963 to 1967—with considerable improvement in our overall results—from 19% to 55% (Table II). The effect of cytotoxics is better illustrated by correlating the results with the stage of the tumours. Table III shows that there has been an improvement in all stages, but particularly in the more advanced cases.

TABLE II. CYTOTOXIC THERAPY

Cytotoxics	No. of cases	Survivors	Survival rate
Nil (1951 - 58)	**16**	**3**	**19%**
Mustine (1959 - 62)	**9**	**5**	**56%**
Actinomycin D (1963 - 67)	**20**	**11**	**55%**

In recent times long-term cytotoxic therapy given in repeated courses has been favoured by most workers and actinomycin D in a dosage of 75 μg/kg/course has remained the most popular drug. This used to be given in divided doses of 15 μg/kg/day on 5 successive days, but we have found that in undernourished children the daily dose often had alarming toxic effects. We have, therefore, changed to a divided dosage of 10 μg/kg/day on 8 successive days. Many workers have also been favourably impressed by vincristine and are using it either as an alternative to actinomycin D or, more frequently, in addition to actinomycin D.

Since 1968 we have, therefore, employed the following regime:

1. Actinomycin D intra- and peri-operatively in a dosage of 10 μg/kg on 8 successive days starting intra-operatively in those who have immediate nephrectomies and 1 day pre-operatively in those who have pre-operative DXR.
2. This is followed by repeated courses of actinomycin D 10 μg/kg on 8 successive days after 6 weeks and then every 2 - 3 months depending on the blood count for a total period of 12 - 18 months.
3. In patients with recurrence or metastases, vincristine 0·05 mg/kg intravenously is given at weekly intervals in the periods between actinomycin D therapy.

It is still too early to assess the results of this regime since the children have been only followed up for 3 months to 3 years. Suffice it to say that at present 12 of the 20 children (i.e. 60%) are alive and well and that there has been quite remarkable regression of metastases in a number of cases.

TABLE III. EFFECT OF CYTOTOXIC THERAPY ON VARIOUS STAGES

	1951 - 58: No cytotoxics			1959 - 67: Cytotoxics		
Stage	No. of cases	Survivors	Survival rate	No. of cases	Survivors	Survival rate
I	**6**	**2**	**33%**	**13**	**10**	**77%**
II	**4**	**1**	**25%**	**7**	**4**	**57%**
III	**2**	**0**	**0**	**8**	**2**	**25%**
IV	**3**	**0**	**0**	**1**	**0**	**0**
V	**1**	**0**	**0**	—	—	—
Totals	**16**	**3**	**19%**	**29**	**16**	**56%**

SURVIVAL RATES

Our over-all survival rates during the period 1951 - 1967, viz. 42% for all cases treated and 56% for those in whom cytotoxics were used, do not measure up to figures quoted from the USA and UK. There are three possible reasons for this:

The Age of Our Patients

The effect of age on prognosis is shown in Table IV and this experience conforms to that of others, particularly in regard to infants under the age of 1 year where survival rates of 80 - 85% are commonly obtained. Indeed, it is now felt that these infants should be separately classified from the point of view of prognosis and treatment. An unusual feature of our series is the small proportion (5%) of cases under 1 year old. This has improved to 10% since the new regime was introduced in 1968.

TABLE IV. EFFECT OF AGE ON PROGNOSIS

Age	No. of cases	Survivors	Survival rate	
Less than 1 year	3	3	100%	1951 - 1967
12 - 35 months	20	10	50%	
More than 3 years	22	6	27%	
Totals	45	19	42%	
Less than 1 year	2	2	100%	1968 - 1970
12 - 35 months	9	5	55%	
More than 3 years	9	5	55%	
Totals	20	12	60%	

The Advanced Stage of the Tumours

This is illustrated by staging the disease according to the scheme suggested by the Wilm's tumour study group in the USA (Table V). Note that 33% of our cases were beyond stage II, i.e. complete surgical removal was impossible. Also note the marked differences in survival rate between the various stages and that with the new regime 1 patient with stage IV disease is alive and well after 8 months.

The Poor General Health of Our Patients

Malnutrition was common and in 60% of our cases the haemoglobin concentration was below 9 g/100 ml. Furthermore, 3 of the children had active tuberculosis while gastro-enteritis was extremely common in the younger patients. These factors rendered the children poor risks for major surgery, contributed to poor wound healing and made postoperative radiotherapy necessary in many cases. Moreover, malnutrition contributed to at least 6 of the later deaths and in 2 of them autopsy revealed no evidence of tumour!

TABLE V. EFFECT OF STAGE ON PROGNOSIS

Stage	No. of cases	Survivors	Survival rate	
I	19	12	63%	1951 - 1967
II	11	5	45%	
III	10	2	20%	
IV	4	0	0	
V	1	0	0	
Totals	45	19	42%	
I	7	6	86%	1968 - 1970
II	5	3	60%	
III	4	2	50%	
IV	3	1	33%	
V	1	0	0	
Totals	20	12	60%	

PRESENT POLICY OF TREATMENT

Our present treatment regime may be summarized as follows:

1. Pre-operative DXR to 1 200 rads.
2. Nephrectomy covered by actinomycin D 10 μg/kg on 8 successive days.
3. Postoperative DXR 750 - 1 000 rads/week up to a total dose (including the pre-operative dose) as follows:
   Under 1 year—2 000 rads;
   1 to 1½ years—2 500 rads;
   1½ years and over—3 000 rads.
4. Repeated courses of actinomycin D at 6 - 8-week intervals for 12 - 18 months.
5. Single metastases: surgical excision covered by actinomycin D, followed by alternating courses of actinomycin D (as above) and vincristine 0·05 mg/kg at weekly intervals during the intervening period.
6. Multiple metastases: DXR up to 1 250 rads covered by actinomycin D and followed by alternating courses of actinomycin D and vincristine.

This paper is based on the work of the Childhood Tumour Clinic of the University of Cape Town and is a preliminary report on only a small aspect of the work which will be reported in greater detail in the near future. The patients were treated at the Red Cross War Memorial Children's Hospital and Groote Schuur Hospital, Cape Town. As Chairman of the Childhood Tumour Clinic, I wish to express my indebtedness to all members of the Clinic for their various contributions. I also wish to thank the surgeons, radiologists, pathologists and others who have been responsible for the care of the patients at the respective hospitals. My thanks are also due to the Superintendents of the Hospitals for permission to publish the data.