Wilms’s tumour—an improved prognosis

Report of 22 consecutive children seen from 1967–71

JOHN MARTIN and PETER P. RICKHAM*

From Alder Hey Children’s Hospital, Liverpool

Martin, J., and Rickham, P. P. (1974). Archives of Disease in Childhood, 49, 459. Wilms’s tumour—an improved prognosis: report of 22 consecutive children seen from 1967–71. An unselected series of 22 consecutive children with Wilms’s tumour seen during the period 1967–71 is described. The management of the patients consisted of operation, radiotherapy, and chemotherapy in varying combinations. The following guide-lines for treatment are suggested: early operation by a transabdominal approach, abdominal irradiation for most patients, both immediate and maintenance chemotherapy, and aggressive treatment of metastatic disease should it occur. The 2-year disease-free survival figures for this series, in the order of 80%, equals the best previously reported and emphasizes the improved prognosis for children with this tumour.

While operation and irradiation were the standard treatments for Wilms’s tumour, survival rates were usually of the order of 20 to 30%, and in the best series only 40 to 50% (Gross and Neuhauser, 1950; Rickham, 1964). The addition of chemotherapy to the treatment for this tumour has led to a striking improvement in survival figures, particularly those reported from North America where up to 4 out of 5 patients are reported cured by a well co-ordinated programme of operation, irradiation, and chemotherapy (Farber, 1966; Fernbach and Martyn, 1966; Sutow et al., 1970; D’Angio, 1972). Similar results, however, have not previously been reported from Britain and this has led to some scepticism concerning the value of chemotherapy, and, on occasions, an unnecessarily gloomy view of the prognosis for children with this tumour. We report a series of patients seen in the 5-year period 1967–71 to illustrate the improved prognosis.

Patients

22 consecutive children seen with Wilms’s tumour during the 5-year period 1967–71 will be described. This period was chosen as its start coincided with the arrival of one author (J.M.) at the centre, and ended with the departure of the other (P.P.R.). Of the 22 children, all were treated at Alder Hey Children’s Hospital except 3 who were seen by at least one of us at the Royal Liverpool Children’s Hospital. These patients probably represent all cases of Wilms’s tumour diagnosed in this period from Merseyside, the Isle of Man, and a large part of North Wales. Of the 22 patients, 21 are still available to follow-up. The remaining patient moved to East Africa and contact was lost.

In the group were 13 females and 9 males, their ages ranging from 2 months to 10 years. The distribution of patients according to age at diagnosis is shown in the Fig. 16 patients had left-sided tumours and 6 patients had right-sided tumours. There were no bilateral cases. 1 patient had a maternal first cousin with a Wilms’s tumour diagnosed in 1965. 1 other patient has hemihyper trophy, the tumour arising on the contralateral side.

All patients had their tumours staged in a similar

![Figure](http://adc.bmj.com/)

FIG.—Distribution of patients by age at diagnosis.
manner to that used in the current M.R.C. and American National Wilms's Tumour Studies (Table I). The results of this staging are shown in Table II.

**Treatment and results**

**Operation.** All patients had surgical removal of their tumours. 18 patients had an initial nephrectomy. In 4 patients only a biopsy was performed at first, with the definitive operation performed 4 to 6 weeks later, after chemotherapy in 3 patients and radiotherapy in 1. These 4 patients had very large tumours and in 2 cases extensive distant metastases were present at diagnosis. All patients were operated upon by one of three paediatric surgeons. There was 1 death after operation.

**Radiotherapy.** Abdominal irradiation was given to 12 of the 22 children. In 1 child this was before operation for a large tumour, and in the remaining 11 it was after operation. The standard procedure was to irradiate a field to the hemi-abdomen extending from the diaphragm to the pelvic brim and crossing the midline to include all of the spine. The dose used was 3000 rads given over 4 weeks.

No abdominal irradiation was given to 10 children.

**TABLE I**

**Staging for Wilms's tumour**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A well encapsulated tumour which is entirely removed at operation; spillage of the tumour does not take place during operation and there is no involvement of the para-aortic nodes on biopsy</td>
</tr>
<tr>
<td>II</td>
<td>There is extension of the tumour beyond capsule either by local infiltration, extension along the renal vein, or involvement of the para-aortic glands, but where the surgeon believes total removal of macroscopical disease was possible</td>
</tr>
<tr>
<td>III</td>
<td>There is extension of the tumour beyond the capsule and there is spillage of tumour at the operation, or tumour is felt to have been left at the time of operation, or there are peritoneal metastases</td>
</tr>
<tr>
<td>IV</td>
<td>Spread to liver, lungs, bones, or brain found at diagnosis</td>
</tr>
<tr>
<td>V</td>
<td>Bilateral disease</td>
</tr>
</tbody>
</table>

*After M.R.C. Trial Protocol.

**TABLE II**

**Stage of patients at diagnosis**

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients</th>
<th>Percentage</th>
<th>Survivors*</th>
<th>Deaths*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8</td>
<td>36</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>27</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>23</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Excludes patient lost to follow-up.

TABLE III

**Reasons for omitting abdominal irradiation**

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Stage I tumour in patients less than 1 year old</td>
<td>2</td>
</tr>
<tr>
<td>(b) Stage I tumour in patient aged 3 years—very small tumour</td>
<td>1</td>
</tr>
<tr>
<td>(c) Stage I tumour—patient had severe actinomycin D reaction</td>
<td>1</td>
</tr>
<tr>
<td>(d) Stage II tumour—less than 1 year old</td>
<td>1</td>
</tr>
<tr>
<td>(e) Stage II tumour—chickenpox in postoperative period and severe actinomycin D reaction</td>
<td>1</td>
</tr>
<tr>
<td>(f) Stage III tumour—death after operation</td>
<td>1</td>
</tr>
<tr>
<td>(g) Stage IV patients treated by operation and vincristine alone</td>
<td>3</td>
</tr>
</tbody>
</table>

for various reasons, as shown in Table III. Apart from the child who died after operation, these children are alive, well, and tumour free. 2 subsequently developed lung metastases that have been successfully treated. None of these children developed a local recurrence in the abdomen. Irradiation to the lungs was given to 2 children to treat metastatic disease.

**Chemotherapy.** No standard form of chemotherapy was used throughout the 5-year period of this study. In 16 children chemotherapy was started at or before operation. 13 children received actinomycin D in a dose of 60 to 120 mg/kg body weight over a 4- to 10-day period, and 3 children received vincristine 1·5 mg/m² body surface area weekly for 6 to 12 weeks. 6 children had no chemotherapy as part of their initial treatment. 3 of these were less than 1 year old and 3 were excluded from chemotherapy as they were participating in a previous combined North of England trial. Of these 6 children, 3, all stage I, are alive and well, but the other 3, all stage II, developed metastases and 2 died.

Maintenance chemotherapy was administered later in the series to 7 children, 2 stage I, 2 stage II, and 3 stage IV patients. Vincristine was the drug used in 5 children and actinomycin D was used in 2 patients. All 7 are alive, well, and tumour free 24 to 45 months after diagnosis.

**Metastatic disease.** In 3 children haematogenous metastases were present at diagnosis (stage IV). Metastases occurred after diagnosis in 5 children, 3 of whom were originally stage II and 2 stage III. Of this total of 8 children, metastases occurred in the lungs alone in 4 children, in the lungs and liver in 2, and in the liver alone in 2 others.

All 3 stage IV patients were treated with vincristine as an initial course of 6 to 12 weekly injections, followed by courses of 3 weekly injections.
Wilms's tumour— an improved prognosis

at intervals of 3 months. These children are alive and tumour free 44, 32, and 30 months later. One child had a recurrence of lung metastases 4 months after diagnosis, which were then treated with irradiation to the lungs followed by actinomycin D at 3-monthly intervals.

Of the 5 children who developed metastases in the course of their disease, 2 were successfully treated. One child had her lung metastases irradiated and subsequently had four courses of actinomycin D at 3-monthly intervals, the other had two lung metastases resected and then received similar chemotherapy. Two children received no treatment for their metastases at their parents request, and both died. The remaining child died 2 months after developing liver deposits that only partially regressed on actinomycin D. These last 3 children, together with 1 child who died 9 days after an operation for a grossly adherent tumour, accounted for the 4 deaths in the series.

At the present time, 17 of the 21 children still being followed up are well and tumour free from 24 to 80 months after diagnosis. If we exclude the child not available to follow-up, the survival rate is 81%, or, on the assumption the remaining child died, it is still 77%.

Discussion

This small series of 22 consecutive patients illustrates the improving prognosis for children with Wilms's tumour. To achieve optimum results requires the co-ordinated efforts of experienced paediatric surgeons, radiotherapists, and paediatricians with a wide knowledge of chemotherapy.

As a result of our experience we offer the following guide lines for the treatment of this tumour.

1. Early, if not immediate, operation.
2. Abdominal irradiation in all stage II and III patients. Its value for stage I patients is doubtful and in stage IV patients is not established.
3. Immediate chemotherapy at time of operation and subsequent maintenance chemotherapy. Both vincristine and actinomycin D appear effective agents. In our experience vincristine is less toxic.
5. Never give up.

There can be no doubt that operation is essential in every patient. Leedle et al. (1970) found no survivors among those in whom nephrectomy was not performed. Surgical removal of the tumour should be undertaken as soon as possible after establishing the diagnosis. The approach should be via the transabdominal route with early ligation of the renal vessels wherever possible. Nephrectomy should be performed in all cases and, in addition, removal of the perinephric tissues and para-aortic nodes.

Abdominal irradiation has also been considered an essential part of the management of this tumour. There must, however, be some doubt as to whether this is as necessary as has sometimes been thought. In our small series, abdominal irradiation was omitted in 10 children and none subsequently developed a local abdominal recurrence. Abdominal irradiation is not without its side effects, and treatment of right-sided tumours has been shown to cause liver damage, occasionally of a severe nature, in some patients. While realizing that this form of therapy is necessary for many children, there may well be others, especially stage I cases, where it could reasonably be omitted. The current American National Wilms's Tumour Study is assessing the necessity for abdominal irradiation in stage I patients. Our stage IV patients responded very well to chemotherapy and subsequent operation. Irradiation was omitted. This approach will not always be successful but does have the advantage of irradiation still being available to treat any subsequent recurrences, as illustrated by one of our patients.

Although no consistent type of chemotherapy was used in our series, we believe that this form of treatment contributed substantially to our good results. Of our 3 children over 1 year of age who received no chemotherapy, 2 died. Actinomycin D was regarded as the drug of choice for the chemotherapy of Wilms's tumour from its early use by Farber et al. (1960). Vincristine received much less attention, though Sutow, Thurman, and Windmiller (1963) and Vietti et al. (1970) described its value in metastatic disease. Only in the last few years, however, has vincristine been used as part of the standard therapy for this tumour. The relative merits of these two drugs are still being assessed, as in the M.R.C. trial. The present American National Wilms's Tumour Study, besides comparing which of these two agents is more efficient, is attempting to determine if the combination of the two drugs is superior to either used alone.

Wolff et al. (1968) have shown that maintenance chemotherapy with actinomycin D has an advantage over a single initial course in reducing the rate of metastasis, though subsequent retrieval by successful management of metastases was less in the maintenance chemotherapy group (Wolff et al., 1974). We used a form of maintenance chemotherapy for 7 children in our series and all remain well and disease free.

It has been suggested that the use of chemo-
therapy lengthened the period of survival but did not improve the cure rate because of an increase in late recurrences. We have not found this, nor have Wolff et al. (1974) in the follow-up of their patients. Leslie et al. (1970) found that only 4 children developed recurrences later than 2 years from diagnosis in an analysis of 335 cases, 112 of whom had received actinomycin D as part of their therapy.

An aggressive approach to metastatic disease, especially if in the lungs, is desirable. This is often rewarding (Martin and Rickham, 1970). In our series, where children were treated for their metastases, 5 of 6 survive and are tumour free. In 2 of our patients metastases recurred several months after treatment of initial metastatic disease. In both cases further treatment was given and these children are alive, well, and free of disease 66 and 28 months later. These 2 children illustrate the importance of not giving up.

Although the prognosis for children with Wilms's tumour has improved, many questions remain unanswered. Stage I patients do particularly well and may not need to receive as much treatment as at present. The role of radiotherapy is in doubt for some patients and the search for more efficient chemotherapy must continue. With known drugs, the most effective method of administration in terms of dose and timing need to be evaluated. In selected groups of high-risk patients the use of actinomycin D and vincristine together, and possibly combinations with newer agents, such as daunorubicin, may prove valuable. The recent development of national and international trials for patients with this tumour holds out the hope that we may learn more about the most effective way to treat these children, and continue to improve an already much more encouraging prognosis.

We thank our colleagues, Mr. J. H. Johnston, Mr. N. V. Freeman, and Drs. W. B. Dawson and Dorothy Mainwaring, for their part in the management of these children.

REFERENCES


Correspondence to Dr. J. Martin, Department of Child Health, Alder Hey Children's Hospital, Liverpool L12 2AP.

Addendum

Attention of readers is drawn to the therapeutic trial of the treatment of Wilms's tumour now being carried out by the M.R.C.'s Working Party on Embryonal Tumours in Childhood. The aim of the trial is to assess the relative efficacy of vincristine and actinomycin D in the treatment of Wilms's tumour after operation and radiotherapy.

Information concerning the trial may be obtained from the secretaries of the Working Party—Dr. P. Morris Jones, Royal Manchester Children's Hospital, Pendlebury Manchester M27 1AH, and Dr. Dorothy Pearson, Christie Hospital and Holt Radium Institute, Withington, Manchester 20.