PAPERS AND ORIGINALS

Nephroblastoma: treatment during 1970-3 and the effect on survival of inclusion in the first MRC trial

E L LENNOX, C A STILLER, P H MORRIS JONES, L M KINNIER WILSON

British Medical Journal, 1979, **2**, 567-569

Summary and conclusions

In 1970-3 313 children were diagnosed as having nephroblastoma in Great Britain. From the start of the first Medical Research Council nephroblastoma study in October 1970 until the end of 1973, 98 children (57% of all eligible children) were included in the trial. Of the 313 children, 288 (92%) had a nephrectomy, 248 (79%) received a course of radiotherapy, and 267 (85%) were given at least four days' chemotherapy. The three-year survival rate was 58%; the rate among children in the trial (77%) was significantly better than that among children who were eligible for the trial but not included (58%). Children who had nephrectomies at specialised children's and teaching hospitals had a higher survival rate than those treated elsewhere.

All children with nephroblastoma should be treated according to well-defined protocols which take into account the age of the child and the stage of the tumour and include a full course of maintenance chemotherapy.

Introduction

Since the 1950s there has been a continuing improvement in the survival of children with nephroblastoma. The three-year survival rate for 335 children diagnosed in England and Wales during 1962-6 was 32%,[1] and the corresponding rate for 245 children diagnosed in Great Britain during 1968-70 was 47%.[2] This improvement was largely attributable to the adoption of modern techniques of combination therapy.

The first Medical Research Council nephroblastoma study was designed to determine whether actinomycin D or vincristine was the better maintenance agent for preventing recurrent and metastatic disease after primary treatment by nephrectomy, paraoperative actinomycin D, and radiotherapy. The treatment protocol is given in the official report on that trial.[3] Entry to the MRC trial took place from August 1970 until March 1974.

The present study was designed to determine the survival rate for all children with nephroblastoma in Great Britain during the years 1970-3, to identify a group of children who would have been eligible for inclusion in the MRC trial but were not entered, and to compare the treatment and survival rates of this group with those of the trial patients. We have used data collected in the MRC trial, but the interpretations and views are our own.

Patients and methods

The 313 children in the series were ascertained from cancer registrations. Clinical and follow-up data were obtained directly from the consultants or from the Marie Curie-Oxford Survey of Childhood Cancers. All but three of the children in the series were followed up for at least three years. We received death certificates for children dying from cancer up to 31 December 1977, so the three children with a shorter follow-up may, in the absence of a death certificate, be assumed to be alive three years after their initial treatment.

The numbers of children with proved nephroblastoma who were registered in the four years 1970-3 were, respectively, 76, 79, 80, and 78. The overall incidence, sex ratio, and age distribution agree with those reported for a number of other large population-based series.[2]

The diagnosis was confirmed histologically in 302 of the children (96%). In the remaining 11 children either preoperative radiotherapy to reduce tumour size rendered subsequent histology inconclusive or the diagnosis was made radiologically or clinically. There were 302 children with unilateral nephroblastoma (141 right-sided and 161 left-sided), and eight with bilateral tumours. We have no details about which kidney was affected in the remaining three children. The children referred to as having bilateral nephroblastoma are those in

Childhood Cancer Research Group, Department of the Regius Professor of Medicine, University of Oxford, Oxford OX1 3QG
E L LENNOX, MB, CHB, research officer
C A STILLER, BA, MSC, research officer

Royal Manchester Children's Hospital, Manchester M27 1HA
P H MORRIS JONES, FRCP, DCH, senior lecturer in child health (paediatric oncology)

Cancer Epidemiology Research Unit, Birmingham University
L M KINNIER WILSON, BM, BCH, research fellow

whom both kidneys were involved initially. In a further six children subsequent involvement of the other kidney was noted five to 43 months after the original diagnosis was made. Thus there were 14 children in whom the disease at some time affected both kidneys.

Opinions have varied as to the value of histological subclassification as a prognostic indicator.[4 5] Given the absence of detailed histology in many cases, and the difficulty of determining the degree of differentiation of the tumour, we did not analyse the series according to histological type of nephroblastoma. Nevertheless, there were at least five patients with "bone-metastasising renal tumour of childhood," which has a very poor prognosis[6]; four of these five children died.

We have adopted the clinical staging system used by the National Wilms' Tumor Study Group,[7] which was also used in the MRC Nephroblastoma Study. The stage was determined by the surgeon and confirmed by the pathologist. The definitions of the stages are: stage I—tumour confined to the kidney and completely resected; stage II—tumour extended beyond the capsule of the kidney either by local infiltration, extension along the renal vein or involvement of the para-aortic nodes, but complete macroscopical removal achieved; stage III—tumour extending beyond the capsule of the kidney and not completely resected or the operative field contaminated with tumour spilled at operation; stage IV—haematogenous metastases: deposits in liver, lung, bone, brain, or other distant sites; stage V—bilateral renal involvement either initially or later. For our study we restricted the definition of stage V to include only initial bilateral tumours.

Table Im (miniprint) shows the distribution of children at the time of diagnosis by age and stage. The proportion of stage I and II tumours was much higher in those patients aged under 4 years at diagnosis.

INCLUSION IN THE MRC TRIAL

Children aged 1 to 14 years with histologically confirmed unilateral nephroblastoma were eligible for the trial unless at the time of initial treatment they were known to have metastases in the liver or outside the abdominal cavity. Children aged under 1 year when first treated had previously shown survival rates better than those for older patients.[8] Furthermore, it was expected that infants might not withstand the intensive treatment specified in the protocol, and so children aged under 1 year were not included in the MRC trial.

In our study the "ineligible" group included patients who would otherwise have been eligible for inclusion in the MRC trial but died within one month of diagnosis. Of the 108 children in the MRC trial, 98 lived in Great Britain and were first treated before the end of 1973; they were therefore included in our series. From October 1970, when entry to the MRC trial began, until the end of 1973, 57% of all eligible children were included in the trial.

Table Im shows the age distribution at the time of diagnosis for trial and non-trial children. Within the group of eligible patients the proportion of those aged under 7 years at diagnosis who were included in the trial was significantly higher than that of the older children ($\chi^2 = 3{\cdot}92$; DF = 1; $P < 0{\cdot}05$).

Results and comment

TREATMENT

Ninety-two per cent of the children in our series (288) had a nephrectomy. In 21 (7%) of these residual tumour was known to have been left in situ or spillage had occurred. Fourteen (4%) of the children had a laparotomy or biopsy without any attempt to remove the tumour. Nephrectomies were performed at 106 different hospitals: 67% of all operations were performed in 47 teaching and children's hospitals; 16% in 26 general hospitals with over 500 beds; and 17% in 33 other hospitals. More than a third of the nephrectomies were performed at eight of the large teaching hospitals.

A course of radiotherapy was given to 248 (79%) children. There were considerable variations in technique, the field irradiated, the number of fractions, and the overall dose and duration of the course. We considered only the effect of the total tumour dose, which ranged from 500 to 4000 rads. Table IIm shows the doses administered to all patients in the study.

The 52 radiotherapy centres where the children were treated were divided into two groups according to the numbers of children treated during the study period. Ten major centres, which each treated 10 or more children, treated 61% of patients, while 42 other centres that each treated fewer than 10 children treated the remaining 39% of patients. Over 20% of the patients given radiotherapy were treated at two of the major centres.

Table IIm also shows the total tumour dose administered to patients eligible for the MRC trial who were treated at the two categories of radiotherapy centre. There was no evidence of a difference in dose with the category of hospital giving the treatment.

Altogether 267 (85%) of the children received a course of chemotherapy lasting at least four days. Forty four (45%) of the children in the trial completed two years' treatment with actinomycin D; only 16 (15%) of those eligible but not included in the trial were known to have had actinomycin D chemotherapy of this duration, though another 18 (17%) were given the drug for an unknown length of time. Vincristine was given for two years to 24 (24%) of the trial children; a two-year course was known to have been given to 6 (6%) of the eligible non-trial group, and a further 12 (12%) of these children were given a course of vincristine of unknown length. To some extent these differences in chemotherapy between trial and non-trial patients may have been a consequence of the longer survival of children in the trial.

For the non-trial children it proved impossible in many cases to determine at which hospital decisions regarding chemotherapy were made, especially when repeated courses were given. We did not therefore analyse chemotherapy by treatment centre.

SURVIVAL RATES

Throughout this report all survival rates refer to three-year survival from the date of first treatment unless otherwise specified. In our series 19 (9·5%) of the 199 patients surviving for two years died during the following year, whereas only three (1·7%) of the 180 three-year survivors were known to have died subsequently. Therefore three-year survival rather than two-year survival may reasonably be equated with truly long-term survival in nephroblastoma.

Three-year survival rates are given in table IIIm for all the children in the present study, divided into the following four groups: children included in the MRC trial; eligible children not included in the trial; children under 1 year of age at diagnosis; children aged 1 year and over who were ineligible for the trial for other reasons. Three-year survival rates by age and tumour stage for the trial and eligible non-trial patients are given in table IVm. The overall survival rate of 77% for the trial patients was significantly better than that of 58% for the eligible non-trial patients ($\chi^2 = 7{\cdot}25$; DF = 1; $P < 0{\cdot}01$). When allowance is made for the distribution of age and tumour

MINIPRINT TABLES

Im

TABLE I—*Age distribution of all children by tumour stage and by eligibility for inclusion in MRC trial*

Stage	Age (years)								
	<1	1	2	3	4	5-6	7-9	10-14	Total
I	28	27	24	21	10	14	9	3	136
II	10	10	12	9	7	8	4	0	60
III	3	8	6	7	4	11	4	5	52
IV	0	3	7	6	1	8	7	3	35
V	2	4	1	1	0	0	0	0	8
Not recorded	3	4	3	4	3	4	1	0	22
Total eligible:	0	40	42	37	25	33	17	8	202
In trial	0	19	22	20	12	18	6	1	98
Not in trial	0	21	20	17	13	15	11	7	104
Not eligible	46	16	11	11	4	12	8	3	111
Total	46	56	53	48	29	45	25	11	313

IIm

TABLE II—*Details of radiotherapy for all children*

Group of children and category of radiotherapy centre	Total tumour dose in rads					No record of radiotherapy	Total
	None	<2000	2000-	>3000	Unknown		
Trial group							
Major*		1	7	67			75
Other		0	4	19			23
All		1	11	86			98
Eligible non-trial children							
None	10						10
Major		3	11	16	7		37
Other		8	16	25	8		57
All	10	11	27	41	15		104
Children < 1 year	28	1	5	4	6	2	46
Other ineligible children	20	4	9	9	18	5	65

*Major centres were those treating 10 or more children.

IIIm

TABLE III—*Three-year survival rates for all children*

	Eligible for MRC trial			Ineligible for MRC trial		Total
	Trial	Non-trial	Total	Age 1 yr	Age 1-14 yrs	
Alive	75 (77%)	60 (58%)	135 (67%)	28 (61%)	17 (26%)	180 (58%)
Dead	23	44	67	18	48	133
Total	98	104	202	46	65	313

Vm

TABLE V—*Three-year percentage survival rate by type of hospital at which nephrectomy was carried out*

	Type of hospital			
	Teaching or Children's	Large general	Other	Total
Eligible:				
Trial	78 (65/83)	80 (4/5)	60 (6/10)	77 (75/98)
Non-trial	63 (30/48)	57 (16/28)	50 (14/28)	58 (60/104)
Not eligible:				
<1 yr old	75 (21/28)	20 (1/5)	67 (6/9)	67 (28/42)
Others	35 (12/34)	14 (1/7)	0 (0/3)	30 (13/44)
Total	66 (128/193)	49 (22/45)	52 (26/50)	61 (176/288)

VIm

TABLE VI—*Three-year survival rates for trial and eligible non-trial children given radiotherapy. Results are percentages with numbers in parentheses*

	Radiotherapy centre		Total
	Major	Other	
Trial	77 (58/75)	74 (17/23)	77 (75/98)
Non-trial	62 (23/37)	56 (32/57)	59 (55/94)
All eligible children	72 (81/112)	61 (49/80)	68 (130/192)

IVm

TABLE IV—*Three-year survival rates by age and stage for trial and eligible non-trial children*

	Stage I and II			Stage III			Total		
Age (years)	1-3	4-14	Total	1-3	4-14	Total	1-3	4-14	Total
Trial:	46	23	69	15	14	29	61	37	98
Alive	37 (80%)	19 (83%)	56 (81%)	11 (73%)	8 (57%)	19 (66%)	48 (79%)	27 (73%)	75 (77%)
Dead	9	4	13	4	6	10	13	10	23
Non-trial:	52	32	84	6	14	20	58	46	104
Alive	39 (75%)	16 (50%)	55 (65%)	0 (0%)	5 (36%)	5 (25%)	39 (67%)	21 (46%)	60 (58%)
Dead	13	16	29	6	9	15	19	25	44
All eligible children:	98	55	153	21	28	49	119	83	202
Alive	76 (78%)	35 (64%)	111 (73%)	11 (52%)	13 (46%)	24 (49%)	87 (73%)	48 (58%)	135 (67%)
Dead	22	20	42	10	15	25	32	35	67

stage among the trial and non-trial patients the difference in survival rates between the two groups was even more pronounced ($\chi^2 = 11{\cdot}67$; DF = 1; $P < 0{\cdot}001$). For the younger children with stage I or II tumours there was little apparent advantage attached to being included in the trial. But the survival of older stage I and II patients in the trial was significantly better than that achieved outside the trial ($\chi^2 = 4{\cdot}82$; DF = 1; $P < 0{\cdot}05$). Among the eligible children with stage III tumours the survival rate obtained within the trial was 66% compared with 25% for those not in the trial—a statistically significant difference ($\chi^2 = 6{\cdot}24$; DF = 1; $P < 0{\cdot}02$).

Table Vm shows the percentage survival rates for each type of hospital at which nephrectomies were performed. The highest overall survival rate was found in the specialised children's and teaching hospitals. Within each category of hospital the children in the MRC trial had a higher survival rate than those who were eligible but not included.

With regard to radiotherapy, we decided not to analyse the effect of total tumour dose on the survival of the trial patients, as the treatment given to the 12 patients who received under 3000 rads deviated from the trial protocol. Among the eligible non-trial patients there was a slight suggestion that a higher survival rate may have been associated with a higher dose of radiation; but the difference in survival rates between the patients who received a total tumour dose of 2000 to 3000 rads and those who were given 3000 rads or more fell far short of statistical significance.

Table VIm shows the survival rates obtained for each category of radiotherapy centre. The rates for centres which treated 10 or more children with nephroblastoma during the study period were only slightly higher, and the difference between the two categories, allowing for the greater proportion of trial patients treated at these centres, was not statistically significant.

Discussion

Inclusion in the MRC trial significantly improved the chances of survival of children with nephroblastoma. If the results are stated in terms of mortality rather than survival rates over the three years after diagnosis there was an overall death rate of 23% for the trial patients compared with 42% among eligible non-trial patients. This difference between the trial and eligible non-trial patients represented a reduction of 45% in the mortality rate for children who were included in the trial.

The improvement in survival for trial patients was spread over all age groups and tumour stages. The poorer survival associated with increasing age which was observed outside the trial was not found within it for children with stage I or II tumours.

No definite conclusions may be drawn from our data on the comparative benefits of different doses of radiotherapy. Other studies have, however, suggested that radiotherapy may be completely omitted from the treatment of children aged under 2 years with stage I tumours without adversely affecting survival[7] or even that radiotherapy is not necessary for patients of any age with this tumour stage.[9]

The concentration of trial patients at the teaching and children's hospitals only partly accounts for the higher survival rates of children who underwent surgery at these hospitals. The more favourable prognosis of trial patients applied both to those treated at specialist centres and to those who were treated at other hospitals. The difference in survival rates between the categories of radiotherapy centre was found to be very slight when account was taken of the fact that a greater proportion of trial patients was treated at the centres which saw a larger number of children with nephroblastoma.

The chances of achieving long-term survival are probably greatly increased by the patients' receiving a full course of maintenance chemotherapy. In the absence of fuller data on the treatment of eligible non-trial patients it is impossible to tell how many of them were given two years' chemotherapy. Clearly, however, such a course of treatment was given to a lower proportion of this group of children than of the trial patients, for whom it formed part of the protocol.

During 1962-9 in Great Britain the three-year survival rate for children with nephroblastoma aged under 1 year at diagnosis was 45%, while the corresponding rate for children aged 1 to 15 years was 32% (Childhood Cancer Research Group, unpublished observations). During 1970-3 the three-year survival rates for the two age groups were, respectively, 61% and 57%. Thus the improvement in the survival rate for children aged over 1 year was substantially greater than that achieved for those under 1 year of age. These very young children were not included in the MRC trial, and a lower proportion of those in our series received intensive therapy compared with the older children. Nevertheless, any statement concerning the survival of infants with nephroblastoma should be treated with caution because of the unknown proportion of such patients who may in fact have had mesoblastic nephromas or other benign renal tumours.

The main conclusion to be drawn from our results and those of trials reported elsewhere is that all children with nephroblastoma should be treated according to well-defined protocols which take into account the age of the child and the stage of the tumour and which include a full course of maintenance chemotherapy.

We acknowledge with gratitude the work of members of the MRC Working Party on Embryonal Tumours in Childhood (listed in ref [3]), especially Dr A Johnson, and also of the many consultants and general practitioners who provided information on which this paper is based. We also thank Dr G J Draper for his advice and for his help in writing this paper, Mrs E M Roberts for her part in the collection of the medical records and for secretarial help, Mrs J Learney for secretarial help, and Mr B Lennox for coding the data for analysis.

We are grateful to the Medical Research Council for permission to use data from the nephroblastoma trial.

The Childhood Cancer Research Group is supported by the Department of Health and Social Security and the Scottish Home and Health Department. Collection of data was also supported by the Marie Curie Memorial Foundation.

References

1 Ledlie, E M, *et al*, *British Medical Journal*, 1970, **4**, 195.
2 Draper, G J, *et al*, *Childhood Cancer in Britain 1953-75*. To be published.
3 Medical Research Council's Working Party on Embryonal Tumours in Childhood, *Archives of Disease in Childhood*, 1978, **53**, 112.
4 Marsden, H B, and Steward, J K, *Tumours in Children*, Recent Results in Cancer Research, Vol 13, p 332. Berlin, Springer-Verlag, 1976.
5 Jereb, B, and Sandstedt, B, *Cancer*, 1973, **31**, 1473.
6 Marsden, H B, and Lawler, W, *British Journal of Cancer*, 1978, **38**, 437.
7 D'Angio, G J, *et al*, *Cancer*, 1976, **38**, 633.
8 Johnson, D G, Maceira, F, and Koop, C E, *Journal of Pediatric Surgery*, 1967, **2**, 13.
9 Voûte, P A, *et al*, paper read at 10th Meeting of the International Society of Pediatric Oncology, 1978.

(*Accepted 17 July 1979*)

ONE HUNDRED YEARS AGO In the House of Lords the Earl of Belmore asked the President of the Council whether it was true that swine landed in this country from America had been found affected with trichinosis; and, if so, whether the Government intended to take any precautions against the introduction of this disease.—The Duke of Richmond and Gordon said that, in consequence of reports from abroad, he had caused portions of certain swine brought from America to Liverpool to be submitted to examination by officers of the veterinary department; and he regretted to say the result had been to discover trichinosis in portions of some of the animals. Investigations were being continued; therefore he was unable to say what steps, if any, it would be necessary to take in the matter. He was glad that the question had been put, because it enabled him to caution the public in the matter, and to mention that the best precaution in the way of dealing with the complaint—one so dire in its effects upon the human species—was to well cook all portions of swine. whether ham, pork, or bacon, before they were made use of. (*British Medical Journal*, 1879.)