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Multimodal treatment in the management of paediatric malignancies in Sri Lanka

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Introduction

Childhood cancers form a specific group of tumours which differ markedly in clinical behaviour, histology and sites of origin. In the last decade, childhood mortality from infections and congenital diseases has been so greatly reduced that cancers, albeit rare, are the second principal cause of death. Only accidents cause more deaths in children less than 12 years of age in Sri Lanka. Childhood cancers make up 2% of all cancers in Sri Lanka. 50% of them are haematological. The epithelial tumours of adult life are rare in children and the spectrum of malignancies in childhood is not varied as seen in adult population. The common types of tumours of childhood, number less than a dozen.

History records some solid tumours undergoing spontaneous remission. Neuroblastoma, hepatoblastoma, and sacrococcygeal tumours are some of them. Nasopharyngeal carcinoma, hepatocellular carcinoma, and Ewings Sarcoma are tumours children share with adults. Genetic factors account for several childhood tumours. Few are associated with chromosomal abnormalities. Such modes of genetic oncogenesis appear to occur in patients with retinoblastoma, Wilms tumour, osteogenic sarcoma, hepatoblastoma and rhabdomyosarcoma.

Some genetic disorders are associated with increased incidence of cancer, e.g. Trisomy 21 has increased incidence of acute lymphoblastic leukaemia. With the use of combined modalities of treatment, such as surgery, radiation therapy and multi-agent chemotherapy over 65% of children with cancer will be cured of their disease. This means that by the year 2000 an estimated one out of 900 young adults will be survivors of childhood cancer[1]. There has been tremendous advances during the last two decades in the management of paediatric cancers. This has resulted from:

- Successive clinical trials of new treatment strategies, based upon the best treatment known at that time.
- The success brought about by the rational combination of the three important therapeutic modalities - surgery, radiotherapy and chemotherapy.
- The dawn of multi-disciplinary team approach.
- The growth of specialized centres of management for children with cancer i.e. Institutions expecting to provide state of the art care for children with cancer. They have teams consisting of experts as well as coordinated programmes for total management.
- The use of rational study protocol.

All of the above factors have become norms of management. The state of the art care is well seen in the USA. 75% of children with cancer are treated according to a national study protocol. Although cure is being achieved in an increasing number of children, the late effects from these treatments have been identified in a significant number of survivors. As this population of children and young adults continue to increase, the need for health professionals, both specialist and primary care practitioners to monitor and treat long term survivors, has greatly increased.

Aims of the study

This study spans from 1975 to 1999. From 1980 to 1995 data of all patients visiting the Institute was correctly recorded; this number included 1959 cases. The purpose of this study was to:

- Present the data available from the National Cancer Institute, Maharagama, Paediatric Oncology Unit, in relation to types of malignancy, age at presentation, the frequency and the ethnic distribution.
- Study the results of treatment and cure and compare them with international results.
- Record complications and late effects due to treatment.

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Material and methods

1959 cases have been entered into this study and all of them have undergone standard investigation and treatment according to international protocols. Certain special investigations such as CT scans MRI scans, routine bone scans and tumour markers were not done as these facilities were not available. Pathology reports which were sent from district and provincial hospitals were all reviewed by the Cancer Institute Pathologist for verification before treatment. Bone marrow examinations were repeated and verified. Acute Lymphoblastic Leukaemia (ALL) was distinguished from Non-Hodgkin's Lymphoma (NHL) on the percentage of blasts at the time of diagnosis using Murphy's classification[2]. More than or equal to 25% blasts indicated ALL and less than 25% NHL. Main disease groups were defined using an altered ICDO classification scheme as it is commonly used in paediatric cancer[3].

In Sri Lanka the upper limit of the paediatric age is 12 years, Hence in this series the age group is classified as below 1 year, 1 to 4 years, 5 to 8 years and 9 to 12 years. There were 1156 (59%) male and 803 (41%) female children. 86.8% were Sinhalese, 6.6% Tamil and 6.7% Muslims. 34.4% and 33.6% of the cases were in the 1 to 4 and 5 to 8 year age groups. Except for the below 1 year group others had a male preponderance.

1075 cases (54.9%) were haematological malignancies and 884 (44.1%) were solid tumours and accounted for 38%. NHL was second with 5.6% (Tables 1, 2 and 3). Brain tumours and retinoblastomas accounted for 11.1% and 6.7% respectively. 113 (5.7%) were classed as 'Others'. This group was separated into 'Frequent' and 'Infrequent' types. Ovarian cancers stood out at 2.3%. Epithelial cancers were rare and less than 1%.

Table 1
Paediatric malignancies in Sri Lanka:
Distribution of malignancies (RSJ/1999)

Type	*Number*	*%*
Haematological	1075	54.9
Solid tumours	884	44.1

Table 2
Paediatric malignancies in Sri Lanka:
Distribution of haematological malignancies (RSJ/1999)

Type	*Number*	*%*
ALL	744	38
AML	107	5.5
NHL	111	5.7
HD	81	4.1
AUL	14	0.7
MDS	3	0.15
CML	15	0.7

Table 3
Paediatric malignancies in Sri Lanka:
Distribution of solid tumours (RSJ/1999)

Type	*Number*	*%*
Brain tumours	218	11.15
Retinoblastoma	132	6.7
Soft tissue sarcoma	112	5.7
Wilms tumour	101	5.0
Neuroblastoma	77	3.9
Bone tumours	91	4.6
Histiocytosis-X	40	2.0
Others	117	5.7
Total	884	45.1

Acute Leukaemia

French-American-British (FAB) classification was used to sub type the acute leukaemias. Table 4 shows the sub types in ALL. 304 (40.9%) were grouped as Unclassified. L1 accounted for 39% and L2 18.2%. 87.9% of ALL were Sinhalese and Muslims showed a higher incidence even though the Tamil population was higher. The war in the North may have contributed to this.

Table 4
Sub types of acute lymphoblastic leukaemia (RSJ/1995)

Sub type	*Number*	*%*
L1	296	39.8
L11	138	18.2
L111	08	1.1
Unclassified	304	40.9
Total	744	100

Table 5 shows the age distribution in ALL. 42.7% was in the 1 to 4 age group with a median age of 4.9 years. 50% of acute myeloblastic leukaemias (AML) were unclassified and 30.1% were M4. 42.4% were in the 9 to 12 age group, with a median age of 7.6 years. The presenting age between ALL and AML showed a distinct difference. Once again the Muslim community had a higher representation - 11.3%.

Table 5
Age distribution in acute lymphoblastic leukaemia (RSJ/1995)

Age	*Number*	*%*
Below 1 year	25	3.4
1-4 years	318	42.7
5-8 years	283	38
9-12 years	118	15.9

All the cases of Non-Hodgkin's Lymphomas (NHL) were of the diffuse type with 95.5% having bone marrow involvement (Table 6). Age distribution of

NHL is shown in Table 7. The median age was 7years. Tamils showed a higher incidence than Muslims.

Table 6
Types of Non Hodgkins Lymphoma (NHL) (RSJ/1995)

Type	*Number*	*%*
Follicular	Nil	0
Diffuse	91	81.9
Burkitt	20	18.1
Total	111	100
Bone marrow infiltration	106	95.5

Table 7
NHL – Age distribution (RSJ/1995)

Age	*Number*	*%*
Below 1 year	1	0.9
1-4 years	24	21.6
5-8 years	42	37.8
9-12 years	44	39.6
Total	111	100

Classically Hodgkin's Lymphomas (HL) are grouped into four sub types. However, 25.9% were grouped as unclassified due to the poor status of the slides on reassessment. Mixed cellular sub type was the commonest (25.9%). 91.3% of HL were in the latter half of childhood. 16% of HL were Tamils with Muslims having 9%.

On presentation, brain tumours were categorised into subtentorial 72.5% (158) and supratentorial 27.5% (60) types. In the subtentorial group there were three main types, medulloblastomas 22.5% (49), brain stem glioma 34.4% (75) and posterior fossa astrocytoma 15.6% (34). Nearly 80% of the brain tumours were in the 5 to 12 year age group. Unique feature in the posterior fossa tumours was that it spared the below one year age group. Retinoblastoma, the second commonest childhood solid tumour, made up 6.7% and 80% were unilateral at the time of presentation. Both eyes were equally affected. Unlike brain tumours 81% of retinoblastomas were below 4 years of age. All bilateral tumours were below 4 years of age, suggesting genetic origin. Retinoblastomas occurring above 5 years were unilateral and may have occurred due to spontaneous mutations. All unilateral and some bilateral tumours had enucleation done at the time of referral.

98% of nephroblastomas (Wilms tumours) were unilateral; equal representation was observed from both sides. 80.5% were below the age of 4 years. Histologically, Wilms tumours occurring after the age of 5 years had more of epithelial component. There were two main types of soft tissue sarcomas (STS) - 44.5% were rhabdomyosarcoms and 55.5% were other types. 38.7% of rhabdomyosarcomas originated in the head and neck region, which was the highest individual site. 83.4% of STS were distributed in the 1 to 8 age group. Neuroblastomas were unique in that 63.6% were in the abdominal cavity and in 29.8% the site was unknown. The age distribution was remarkable in that 54.5% were below the age of 4 years.

Except for a solitary case of chondrosarcoma, the rest of the bone tumours were in two groups, Ewing sarcoma 56% and osteogenic sarcoma 43%. 60% of Ewing sarcomas were in long bones, and affected the upper third of the shaft of long bones and rarely showed the 'onion peel' appearance radiologically. Flat bones were affected in 30% and ileum was the common site. In osteogenic sarcomas femur was the disease site in 87.5%. Both Ewing and osteogenic sarcomas were seen in the second half of childhood.

There were 40 cases Langerhan cell histiocytosis; however the sub types affected different age groups (Tables 8-11). Letterrer-Siwe disease was the least common type, where 75% of them were seen in less than one-year age group (Table 9). 90% of Hand-Schuller-Christian Syndrome and 100% of eosinophilic granuloma were found in the second half of childhood (Tables 7 and 8). In the unclassified type 66.6% were in the 5 to 8 year age group (Table 9).

Table 8
Paediatric malignancies in Sri Lanka: Langerhan-Cell-Histiocytosis (RSJ/1995)

Type	*Number*	*%*
Letterer-Siwe-Disease	4	10
Hand-Schuller-Christian Syndrome	10	25
Eosinophilic granuloma	14	35
Unclassified	12	30
Total	40	100

Table 9
Letterrer-Siwe-Disease - Age distribution

Age	*Number*	*%*
Below 1 year	3	75
1-4 years	1	25
5-8 years	0	0
9-12 years	0	0
Total	4	100

Table 10
Hand-Schuller-Christian-Syndrome Age distribution

Age	*Number*	*%*
Below 1 year	0	0
1-4 years	1	10
5-8 years	6	60
9-12 years	3	30
Total	10	100

Table 11
Eosinophilic Granuloma - Age distribution

Age	*Number*	*%*
Below 1 year	0	0
1-4 years	0	0
5-8 years	4	28.6
9-12 years	10	71.4
Total	14	100

Results

The results of paediatric malignancies have been categorized in to three periods ie.1980 to 1985 - Period 1; 1986 to 1990 - Period 2; 1991 to 1995 - Period 3. This has been done according to the facilities and man power available. During Period 1 there was no Oncology training programme and facilities were minimal. Period 2 saw the dawn of Oncological training programme. Period 3 was blessed with trained Oncologist, Oncology nursing staff and the availability of first CT scanner in the private sector and at the National Hospital, Colombo. National Cancer Institute had the establishment of the Blood Bank and facilities to obtain blood components. The protocols adopted for various conditions underwent change according to the availability of resources. Results have been compiled as Complete Remission (CR), 3 year and 5 year disease free survival. Cases lost for follow up has been indicated as 'lost'. 5 year disease free survival figures has not been given for Period 3. Patients lost ranged from 8 to 23 % in the haematological malignancies and less than 10% for solid tumours.

Remission rates (CR) in haematological malignancies

CR rates for ALL during the three periods are shown in Table 12. Even though the total number of patients differed in the first period, CR rate was low (55.5%), compared to 76% in the second period and 80% in the third period. The protocols adopted were different A similar trend was seen with AML, 37.5% in period 1 and 57.1% and 60% in period 2 and period 3 respectively (Table 13). The management protocols were different. CR rate for NHL in period 1 was half that seen period 2 and period 3 (Table 12). CR rate was 40% vs 81.3% vs 79.2%. 'COP' schedule was used in period 1 and 'CHOP' schedule in the other two periods. The CR rates in Hodgkin's Disease were 42.8%, 69.4% and 78.8% in the three periods respectively. All the cases had chemotherapy irrespective of the stage. Customarily stage 1, Stage 11 A in adults had involved nodal irradiation. 'MOPP' schedule was the standard chemotherapy protocol used during period 1. However this was changed to alternating 'MOPP' with 'ABVD'.

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Table 12
Remission rate and survival figures in ALL

Period	*N*	*CR*	*3 year*	*5 year*	*Lost*
1980/1985	90	50/90 55.50%	25/90 27.70%	22/90 24.40%	22%
1986/1990	296	225/296 76%	118/296 39.80%	110/296 37.90%	17%
1991/1995	280	224/280 80%	145/280 51 .80%		16%
Total	666	499/666 75%	288/666 43.20%		17%

Table 13
Remission rate and survival figures in AML

Period	*N*	*CR*	*3 year*	*5 year*	*Lost*
1980/1985	8	3/8 37.50%	Nil	Nil	Nil
1986/1990	43	22/43 51.10%	10/43 23.20%	4/43 9.30%	11.6%
1991/1995	75	45/75 60%	20/70 26.60%		16%
Total	126	70/126 55.50%	20/126 23.80%		13.5%

Three and five year survival figures

In ALL and NHL remission induction was followed by consolidation, CNS prophylaxis and maintenance therapy for three years. Hodgkin's Lymphoma had only remission induction therapy. ALL and NHL had the same CNS prophylaxis and maintenance schedule - 5. In AML routine CNS prophylaxis was not given. Maintenance therapy was given for one year in period 1 and for two years in periods 2 and 3. Management of solid tumours involved utilization of all three modalities of treatment. Except for brain tumours all others had

chemotherapy up-front. Chemotherapy was used for two years. Termination of chemotherapy was dependant on the status of bone marrow.

ALL, the commonest malignancy in children, had improvement of three-year survival from period 1 to 3, the recorded figures being 27.7% to 39.8% to 51.8%. Once uncomplicated survival was completed by three years, they had greater than 90% chance of surviving 5 years. Lost for follow up during period 1 was up to 22% (Table 12). There were no survivors in AML in period 1 and no significant three-year survival difference between the periods 2 and 3 (23.2% vs. 26.6%). Only 9.3% survived 5 years. In period 3 children lost for follow up was the same for ALL and AML (Table 13). NHL showed a definite difference in 3 year survival from period 1 to period 3, with different induction schedules 33% to 79% with 22 to 23% lost for follow up (Table 14). In Hodgkin's Lymphoma the 3 year and 5 year survival was the same 28% and 55.5%. This is an indication that if HL children survived 3 years disease free, then they had the same chance of surviving 5 years. On this assumption 73.6% successfully treated HL children will survive 5 years irrespective of the stage (Table 15).

Table 14
Remission rate and survival figures in NHL

Period	*N*	*CR*	*3 year*	*5 year*	*Lost*
1980/1985	15	6/15 40%	5/15 33 30%	5/15 33.30%	20%
1986/1990	43	35/43 81 .30%	34/43 79%	30/43 69%	23.2%
1991/1995	53	42/53 79.20%	42/53 79.20%		22.5%
Total	111	83/111 74.70%	27/37 72.90%		22.5%

Table 15
Remission rate and survival figures in HL

Period	*N*	*CR*	*3 year*	*5 year*	*Lost*
1980/1985	7	3/7 42.80%	2/7 28%	2/7 28%	Nil
1986/1990	36	25/36 69.40%	20/36 55.50%	20/36 55.50%	8.3%
1991/1995	38	30/38 78.90%	28/38 73.60%		10.5%
Total	81	58/81 71.60%	50/81 61.70%		8.6%

In brain tumours, chemotherapy schedules were different in period 1 and period 2. Medulloblastoma showed a significant difference in three year survival rates in the three periods from 40% to 46.6% to 58.2% (Table 16). Brain-Stem-Gliomas (BSG) during period 3 was diagnosed on CT scans and none had surgery; all had chemotherapy followed by radiation therapy. In periods 1 and 2, diagnosis was made on radiology, worsening clinical signs and on patients who did not respond to anti TB drugs. They were unfit to have any chemotherapy and only radiation therapy. None survived 3 years in period 1 and 10% (2/20) survived 3 years in period 2. There were no 5 year survivors. Period 3 had 26.6% (12/45) surviving 3 years which is more than double that seen in period 2 (Table 17). Posterior fossa astrocytoma had the best survival figures for brain tumours. 60% three-year survival was seen in periods 2 and 3 and 30% survived 5 years in period 2 (Table 18). Supra tentorial tumours ranged from craniopharyngiomas to gliomas and choroid plexus tumours. They had surgery followed by radiation therapy and had an overall three year survival figure of 55% (Table 19).

Table 16
Survival figures in brain tumours – medulloblastomas

Period	*N*	*3 year*	*5 year*
1980/1985	10	04/10 (40.0%)	3/10 (30.0%)
1986/1990	15	07/15 (46.6%)	5/15 (33.3%)
1991/1995	24	14/24 (58.2%)	
Total	49	25/49 (51.0%)	

Table 17
Survival figures in brain tumours – BSG

Period	*N*	*3 year*	*5 year*
1980/1985	10	Nil	Nil
1986/1990	20	02/20 (10.0%)	Nil
1991/1995	45	12/45 (26.6%)	
Total	75	14/75 (18.6%)	

Table 18
Survival figures in brain tumours –posterior fossa astrocytoma

Period	*N*	*3 year*	*5 year*
1980/1985	04	01/04 (25%)	Nil
1986/1990	10	06/10 (60%)	03/10 (30%)
1991/1995	20	12/20 (60%)	
Total	34	19/34 (56%)	

Table 19
Survival figures in supra tentorial brain tumours

Period	*N*	*3 year*	*5 year*
1980/1985	08	03/08 (37.5%)	02/08 (25%)
1986/1990	20	10/20 (20.0%)	06/20 (40%)
1991/1995	32	20/32 (62.5%)	
Total	60	33/60 (55.0%)	

Treatment of retinoblastoma was a success story when figures are compared in the different periods. All unilateral tumours had routine enucleation and bilateral tumours had enucleation of the worst affected eye. In period 1 all had oral cyclophosphamide with or without radiation therapy. Due to the alarming survival figures in period 1, treatment protocol was changed. With the change of protocol 5 year survival rose from 17% in period 1 to 54.9% in period 2. Three-year survival in period 3 was 69.5% (Table 20). Survival figures in Wilms tumours is shown in Table 21. Changes in survival rates are due to changed management protocol. In period 1 patients had six weekly Actinomycin D for one year postoperatively. In periods 2 and 3, children had Actinomycin D during surgery and postoperatively in combination with doxorubicin for a year. Radiotherapy was given in indicated cases only. Five-year survival changed from 52.3% to 65.5% from period 1 to 2. Three-year survival rate of 78.5% was seen in period 3. Cases lost for Wilms tumour was less than 4%. In Wilms tumour there was one case with aniridia and one with hemihypertrophy of the body; both cases died within one year. In soft tissue sarcoma, the 110 cases recorded are confined to periods 2 and 3. Abdominal rhabdomyosarcomas did poorly as all of them were referred after inadequate surgery and most patients were not fit to have chemotherapy. There were no 5 year survivals and the three year survival was confined to 8.3%. On the other hand head and neck rhabdomyosarcomas did better with the combined modality of treatment with three year and five year survival figures of 39% and 26% respectively. Other soft tissue sarcomas had survival figures of 36% and 24.5% at three and five years respectively.

Table 20
Survival figures in retinoblastoma

Period	*N*	*3 year*	*5 year*	*Lost*
1980/1985	35	10/35 (28.5%)	07/35 (17.0%)	14.2%
1986/1990	51	35/51 (68.6%)	28/51 (54.9%)	13.7%
1991/1995	46	32/46 (69.5%)		17.3%
Total	132	77/132 (58.3%)		15.1%

Table 21
Survival figures in Wilms tumour

Period	*N*	*3 year*	*5 year*	*Lost*
1980/1985	21	12/21 (57.1%)	11/21 (52.3%)	Nil
1986/1990	52	36/52 (69.2%)	34/42 (65.5%)	3.8%
1991/1995	28	22/28 (78.5%)		3.5%
Total	101	70/101 (69.3%)		2.9%

In Neuroblastoma, too, the management protocol differed in the three periods. In periods 1 and 2 the five year survival was almost half the figure seen in the three year period, showing that almost 50% developed recurrent disease once being in remission and clinically disease free at three years (Table 22). Results of management's of bone tumours in period 1 was dismal, basically due to inability to give high dose methotrexate with folinic acid rescue in osteogenic sarcoma. Schedule variation was seen in periods 2 and 3 with change in survival.

Table 22
Survival figures in neuroblastoma

Period	*N*	*3 year*	*5 year*
1980/1985	05	03/15 (20.0%)	02/15 (13.3%)
1986/1990	30	20/30 (66.6%)	10/30 (33.3%)
1991/1995	32	22/32 (68.7%)	
Total	77	45/75 (58.4%)	

Three-year survival of 44.4% and 43.3% was seen Ewing sarcoma and osteogenic sarcoma respectively. In Langerhan cell histiocytosis 72.9% overall three-year survival was seen with eosinophilic granuloma having 100% survival (Table 23). In frequent paediatric malignancies gonadal tumours had the best survival figure, 62.5% three-year survival, nasopharyngeal carcinoma having 54.5%.

Table 23
Survival figures in Langerhan-cell histiocytosis

Type	*N*	*3 year*
Letterer-Siwe-Disease	04	Nil
Hand-Schuller-Christian Syndrome	10	08/10 (80%)
Eosinophilic granuloma	14	14/14 (100%)
Unclassified	12	07/12 (70%)
Total	40	29/40 (72.5%)

Discussion

Childhood cancers are rare, but with modern treatment a high cure rate can be expected. The same cannot be said for adult cancers. This has been possible because a team approach that incorporate the skills of the paediatrician, paediatric surgeon, radiation oncologist, paediatric medical oncologist, haematologist, rehabilitation specialist and social workers are imperative to ensure that patients receive treatment, supportive care and rehabilitation in order to ensure optimal survival and quality of life. This type of 'state of the art' treatment should be given at specialized centres, using protocols that have been tried out and proved effective.

Approximately 70% of children with ALL are cured with current protocol-based treatments, while 95% of the patients can be expected to attain complete remission[4]. Cure is correlated to a number of prognostic variables. These include clinical parameters and biologic variables. With the limited resources available we have been able outline the clinical variables. For the same reason the aggressiveness of the induction schedules used in the treatment. Hence our CR rate being 80% and a cure of 37.5% in period 2 and three year survival of 51.8% in period 3. Apart from bone marrow relapse, recurrent CNS disease was the major complication that was encountered. In a follow up of 593 cases of ALL 40 (6.7%) had recurrent CNS disease. Majority was in ALL (L3-25%). Table 24 shows the different types of CNS disease. Meningeal leukaemia accounted for 80%. Tables 25 and 26 shows the survival after recurrent CNS disease and the survival of sub types. Only 25 % survived over one year. The survival figures for AML were dismal - 9.3% 5 year survival in period 2 and 26.6% three year survival in period 3. United Kingdom national statistics show survival in AML has improved from 8% at 4 to 5 years during 1974-1976 to 25% from 1983-1985[5]. With more aggressive chemotherapy recent disease free survival has risen to 30 to 40%[6]. Majority of them need bone marrow transplants if we are to achieve a high cure rate. Rate of cure after transplant is 60 to 70%[7].

Table 24
Incidence of sub-types of recurrent CNS disease

Type	*N*	*Prevalence*
Meningeal leukaemia	32	80%
Hypothalamic syndrome	05	12.5%
Localized CNS disease	03	7.5%
Total	40	100%

Table 25
Survival figures in recurrent CNS disease

Duration	*N*	*Prevalence*
< 1 month	04	10%
1-6 months	15	37.5%
6-12 months	11	27.5%
> 1 year	10	25%
Total	40	100%

Table 26
Survival of sub types of R-CNS disease after treatment

Duration	*Meningeal leukaemia 32 Cases*	*Hypothalamic syndrome 5 Cases*	*Localized disease 3 Cases*
< 1 month	01	Nil	Nil
1-6 months	11	02	02
6-12 months	10	01	Nil
> 12 months	07 (21.8%)	02 (40%)	01 (33%)

We have had excellent survival figures for NHL i.e. a cure rate of 69%, with most studies reporting over 60% cure rate[8]. A possible reason may be the use of 'CHOP' schedule with routine CNS prophylaxis and maintenance therapy for three years, as we now know that 'CHOP' is the best schedule for NHL. More than 75% of newly diagnosed HL in children are cured with modern radiation therapy and/or combination therapy[9]. Our results show 55.5% 5 year survival in period 2 and 73.6% three year survival in period 3, using combination chemotherapy alone. Use of combination chemotherapy judiciously has spared muscle atrophy that can occur with the use of radiation therapy.

Primary brain tumours are a widely varying group of diseases and form the most common solid tumours in children. The clinical distribution of these tumours does not vary globally and more than 50% of children diagnosed with brain tumours will survive 5 years from diagnosis[10]. For a good many of childhood brain tumours, the optimal treatment regimen has not been determined. In this series for medulloblastomas and BSG the chemotherapy schedule was changed from vincristine + procarbazine + methyl CCNU to 8-drugs-in-one-day-regime ("8 in 1") and immediate survival advantage was seen. In medulloblastoma from 40% three year survival in period 1 to 58.2% in period 3. In BSG no survival in period 1 to 26.6% three year survival in period 3. BSG is classified according to location, extent of spread and histology. BSG may occur in pons, mid brain, the tectum, the cervico-medullary junction, or the dorsum as exophytic growths. However, majority are in the pons and are diffuse and intrinsic. One third spread by the CSF channel. The less common tumours of mid brain, especially in the tectal plates, have slow growth and long term survival. There is approximately 80% five year progression free survival vs. 20% for tumours in pons and medulla[11]. All the BSG were treated without a biopsy; however biopsy may be indicated for BSG that are not diffuse and intrinsic, when the tumour is progressive or when surgical debulking is possible. New approaches with stereotactic needle biopsy may make biopsy safer. These facilities were not available in Sri Lanka during this study.

Majority of patients with retinoblastoma have extensive disease within the eye at diagnosis with either massive tumour involving more than one half of retina, multiple tumours diffusely involving the retina, or obvious seeding of the vitreous. The goals of therapy are two fold; to cure the disease and to preserve as much vision as possible. In this series cases referred were after enucleation and 3 year survival increased from 28.5% to 69.5% basically because all had intrathecal methotrexate with combination chemotherapy. CNS seeding was the primary site of disease recurrence and with the new approach of treatment CNS seeding was overcome. Patients with retinoblastoma, particularly the hereditary type, have an increased frequency of second malignancies, most often bone tumours, occurring in up to 8% after 18 years of follow-up[12]. Wilms tumour is a curable condition in the majority of affected children. Greater than 90% of patients survive 4 years after diagnosis[13]. Our series recorded 78.5% three-year disease free survival in all cases pooled together. The major drawback in this series was the absence of data on the subtypes and operative findings and inability to recover the original slides of second opinion. Pathologist's reluctance to release slides for second opinion remained an obstacle in obtaining good histological reports. This was true for all solid tumours. Paediatric surgeons other than at Lady Ridgeway Children's Hospital carried out surgery without consultation with the Oncologists and patients never had Actinomycin-D during surgery. Post surgical management was according to international protocol; hence the lower survival figure is because of inadequate staging and proper subtyping.

Nearly 70% of neuroblastoma patients have metastatic disease at diagnosis[14] and it is of paramount importance to identify them and to see the extent of disease prior to treatment. It is also necessary to perform catecholamine assays in urine prior to and during management. MIBG scan facilities were not available in Sri Lanka and catecholamine assays took nearly a month, which would mean that the disease will become far too advanced if this test was done on a routine basis. In spite of this, by adopting a established protocol it was possible to cure one third of the patients during period 2 and to a 68.7% three year survival in period 3. According to children cancer group (CCG) staging system, stages I, II, III, (unresected negative nodes) the probability of long term survival is 75 to 90% depending on the age and for stage IV 50% to 70%[15,16].

90% of patients with apparently localized Ewing sarcoma have occult metastatic disease[17] and survival is poor if an aggressive treatment approach is not adopted. This is quite evidently seen in our series. There were no

survivors in period 1. In periods 2 and 3 survival rates improved and in period 3 the philosophy of radical surgery for "expendable bones" (like the fibula) was adopted. This reduced the tumour burden and better results were seen with chemotherapy. Hence, three-year survival figure of 44.4% in period 3. Soft tissue sarcomas (STS) consists of a malignant tumour presumably originating in the primitive mesenchymal tissue and exhibiting no rhabdomyoblastic differentiation formed a definite entity when compared to rhabdomyosarcoma. Abdominal rhabdomyosarcomas did poorly as almost all the tumours were inadequately debulked, resulting in a large tumour burden. There were no 5 year survival in this group. CNS extension has been reported as a complication in head and neck rhabdomyosarcomas, none were seen in this series; however their presentation is late. 26% five year survival was seen in this group. It is reported to be more than 60% in those children who receive optimal treatment[18]. Our results are way below the best figures given, in view of the late presentation and lack team management.

Osteogenic sarcoma was one other tumour that had dismal survival figures in our series - 43.3% three year survival in period 3. Patients who survived were those consented to amputation/disarticulation as these cases had extensive tumours. Presentation was late because all were treated by Ayurvedic practitioners.

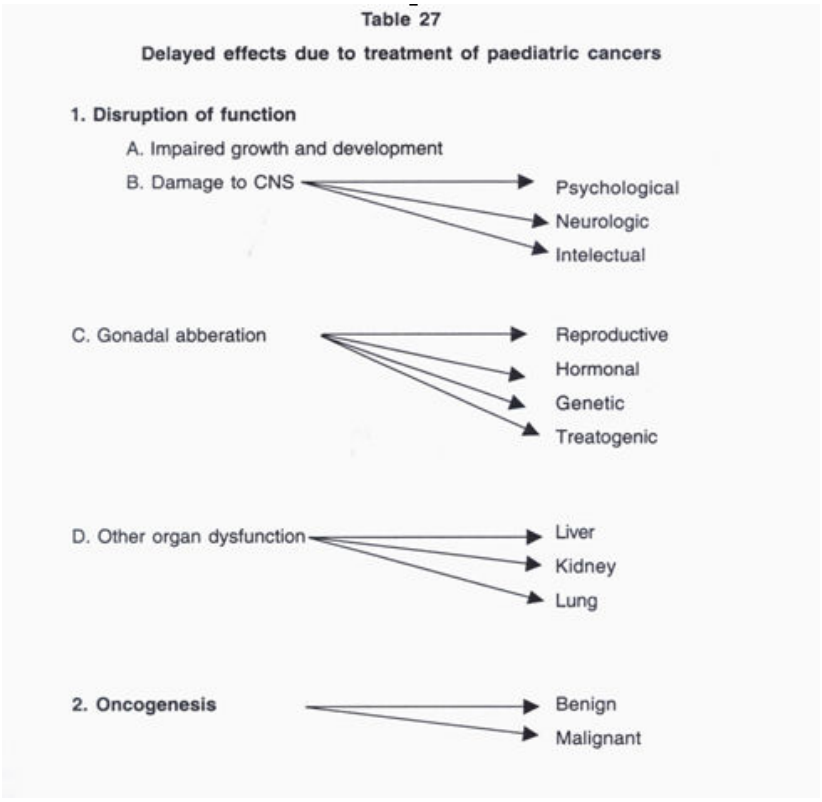
Our experience with limited number of nasopharyngeal cancer is that they remained local and loco-regional. Systemic spread was not seen and 54.5% survived 3 years. Yolk sac tumours were extensive (Stage III/IV) and all had inadequate debulking and were uncontrollable with chemotherapy. Different results were seen with gonadal ovarian tumours. Dysgerminomas gave good results with radiation therapy. No chemotherapy was used in the treatment of the latter.

Langerhan-cell-histiocytosis gave mixed results. As classically stated, eosinophilic granuloma was treated with surgical 'scooping' followed by low dose radiation therapy which gave 100% survival. Low dose radiation therapy had a definite place in the management of 'punched out' areas in bone with 100% local control.

Although cure is being achieved for a sizeable number of children with multimodal therapy, late effects from these treatment have been identified in a significant number of long term survivors. Children withstand all forms of treatment remarkably well; however the late effects will manifest when the child matures. Hence, observation of late effects has been documented in this series 5 years after being pronounced cured. Table 27 outlines the possible delayed effects.

Table 27

Delayed effects due to treatment of paediatric cancers



Linear growth is an important aspect in the growth and development of a child; two factors contribute to this (Table 28). Sixty six children cured of ALL have been compared with normal children using Sri Lankan height/weight chart[18a] (Table 29). 21 (38.2%) boys and 5 (44.5%) girls had growth retardation possibly due to effects of cranial irradiation. Pituitary hormone studies were not done due lack of facilities. Neuropsychological effects have been studied in children who have had cranial prophylaxis and interesting results have been observed (Table 30). A significant proportion of children over 6 years of age (90%) did not attend school, the primary cause being that they were not able to compete with the normal children and 65% of children in this group were not active in school. It is possible that this is a direct effect of the radiation therapy given. Recent investigations have revealed that children treated for ALL were significantly smaller than normal counterparts[19]. It has been suggested that lower height in ALL children was present at diagnosis[20] or consequence of disease. This is consistent with a recent study documenting an abnormality in endocrine function as a manifestation of ALL[21]. Cranial irradiation of doses 2400cGy to children less than 10 years shows an IQ of 85 to 99 - a drop of 10 to 11 points[22]. A proportion of ALL children in this series above 6 years who had this dose of radiation showed inability to compete and was inactive at school. A comparison of cranial irradiation doses of 1800cGy versus 2400cGy has shown normal growth rate and IQ with 1800cGy and not with the latter[23]. Higher doses of radiation to the brain show significant neurological and mental disturbances[24]. 20 to 30% of medulloblastomas receiving higher dose of radiation showed CNS disturbances with up to 50% of them needing special educational institutions[25].

Table 28

Factors that contribute to linear growth of children after multimodal treatment

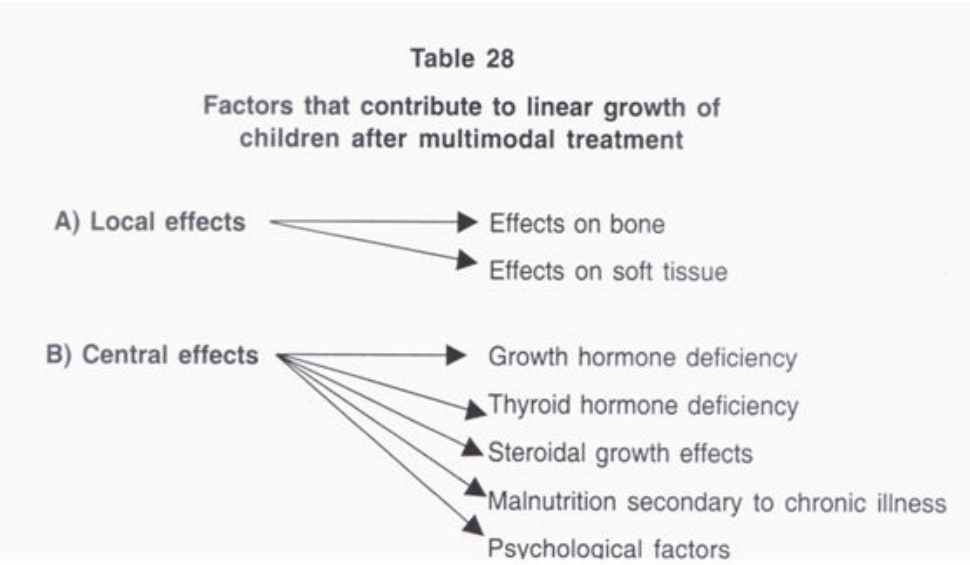


Table 29

Comparison of hights of children with all after CNS prophylaxis, with normal Sri Lanka school children using tentative height for age chart of Lucus et.al.1987

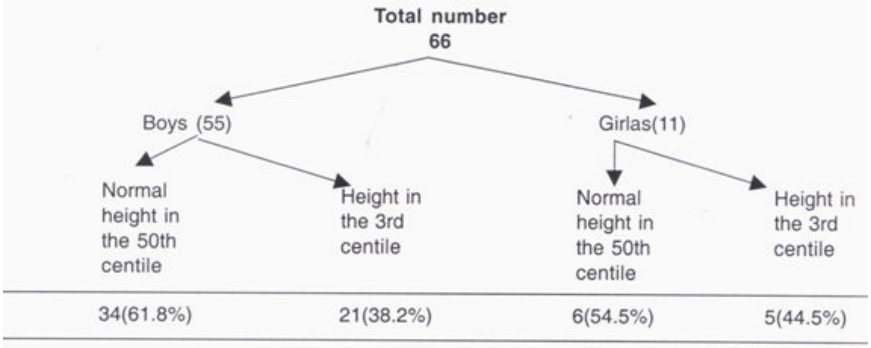


Table 30

Effects of cranial irradiation in children with all 5 years after completion of maintenance therapy

Type of Assessment		*Children less than 6 Yrs. (45) 2000 Cgy in 2 weeks*	*Children over 6 Yrs. (21) 2000 to 24000cGY in 2 Wks.*
1) School performance			
	poor	31%	38%
	Good	40%	23%
	Excellent	13%	33%
2) Behaviour	Normal 55%	38%	
	Aggressive	31%	38%
3) Attending school		60%	10%
4) Not attending school	1	5%	90%
5) School activity			
	Active	80%	35%
	Inactive	20%	65%

In this series all cases of HL had chemotherapy and no endocrine dysfunction was seen. 44% of HL and 17% of NHL had elevated levels of TSH when treated with radiation therapy to the neck with mean interval of occurrence of 18 to 31 months[26].

The cumulative risk of developing a second malignant neoplasm following radiation therapy in long term survivors of childhood cancer has been estimated as high as 10% by 10 years following initial treatment and 17% by 20 years[27,28]. The annual risk of developing second malignancy during or after treatment for ALL is 62.5 per 100.000[29]. Chemotherapy can also produce a second malignancy. In many instances it is difficult to evaluate the precise oncogenic effect as chemotherapy is given before during or after radiation therapy. Both modalities may affect DNA-RNA moieties and nucleic acid metabolism. Both these modalities are also immunosuppressive.

Table 31 shows 1268 cases in this series evaluated, of which 528 (41.6%) cases survived beyond 5 years and 11(2%) had a second malignancy. The types of second malignancies are shown in Table 32.

Acute myelomonocytic leukaemia (AMML) and supratentorial gliomas made up 27.2% each. Characteristically the gliomas were all supratentorial which is not in keeping with classical presentation of brain tumours in children. Table 33 shows the distribution of the second malignancies.

Table 31
Incidence of second malignancy after 7 years of disease free follow up

Total number of cases evaluated	1268
Number of cases surviving 5 years	528 (41.6%)
Number of second malignancies	11 (2%)

Table 32
Types of second malignancy

Type	*N*
Acute myelomonocytic leukaemia (AMML)	3
Gliomas	3
Ewing sarcoma	2
Acute undifferent leukaemia (AUL)	1
Bone sarcoma	1
Follicular carcinoma of thyroid	1
Total	11

Table 33
Distribution of second malignancies

AMML	*Gliomas*	*Ewing Sarcoma*	*AUL*	*Bone Sarcoma*	*Thyroid Ca.*
HD 2	ALL 2	HD 1	HD 1	Retino 1	Retino 1
Retino 1	Wilms 1	Wilms 1			

Children who were treated for HL and retinoblastoma had the highest number of second malignancies viz. 36.3% (4/11). The cumulative risk of second malignancy following treatment for HL in children and adolescents is 18.7% at 15 years after diagnosis, with predominance of bone sarcoma[30]. In our series,

one out of 4 cases were bone sarcomas;Three out of 4 were acute leukaemias. One case of follicular carcinoma was seen in a patient with a retinoblastoma, who had chemotherapy. It has been estimated that 20 to 30% of individuals exposed to external thyroid irradiation had developed single or multiple thyroid nodules; approximately 30% of them are malignant-follicular or mixed types rarely anaplastic. A single case in our series had a bone sarcoma and this was in a case of retinoblastoma. Retinoblastomas are known to get bone sarcomas. All our cases of second malignancies had a fatal outcome within a year in spite of active treatment.

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