THE CENTRAL AFRICAN JOURNAL OF MEDICINE

Vol. 54, Nos. 5/8 May/August 2008

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Owned and Published by the Central African Journal of Medicine in Conjunction with the College of Health Sciences, University of Zimbabwe.

University Of Zimbabwe

Early deaths and other challenges to childhood cancer survival in Ibadan, Nigeria

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Abstract

Objectives: To determine the frequency of early deaths and the associated risk factors in children suffering from cancer at the University College Hospital, Ibadan.
Design: A retrospective study involving review of case notes of children suffering from cancer.
Setting: Department of Paediatrics, University College Hospital, Ibadan, Nigeria.
Subjects: All cases of childhood cancer managed in the Department between January 1998 and December 2004. Inclusion criteria were histological or cytological confirmation of diagnosis, suggestive clinical features and availability of details about the course of the illness.
Main Outcome Measures: Interval between diagnosis and death, rate of early death (death within 30 days of diagnosis) and risk factors for early death.
Results: Eighty eight cases of childhood cancer were seen out of whom 52 died during the period. Four cases with incomplete data were excluded from subsequent statistical analysis. There were 29 (34.5 %) early deaths defined as death within 30 days of diagnosis. The odds of early death were increased in the presence of bilateral kidney involvement, masses in the liver, splenic masses, pulmonary metastasis and stage D of Burkitt lymphoma. Logistic regression analysis revealed that pulmonary metastasis was a significant independent predictor of early death.
Conclusions: Early childhood cancer mortality rate is high. Early diagnosis and referral for appropriate care may reduce childhood cancer mortality in Nigeria.

Cent Afr J Med 2008;54(5/8)32-39

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The ADOC regimen (Doxorubicin, Cisplatin, Vincristin and cyclophosphamide) for invasive malignant thymoma was used in the treatment of the only case of malignant thymoma. [14]

All children diagnosed and managed for cancer in the department between January 1998 and December 2004 was studied. Inclusion criteria were histological or cytological diagnosis of tumour from aspirate or biopsy of tumour mass or bone marrow, radiological evidence of a malignant tumour in addition to suggestive clinical features and availability of details of clinical condition of the child at diagnosis and the clinical course of the illness.

Data Collection.

Data was extracted from the case notes and mortality summary cards of all the children diagnosed and managed for cancer the Department during the study period who met the inclusion criteria. The information extracted included age and sex of each case, the duration of the illness at presentation in the hospital, clinical stage of the disease, and organs affected at presentation. Information was also obtained on the course of the illness with respect to treatment, response to treatment and the time interval between diagnosis and death.

Early death was defined as death within 30 days of diagnosis of the malignant condition and the date of diagnosis was the day on which the diagnostic test that confirmed the diagnosis was done e.g. the day on which fine needle aspiration biopsy or bone marrow aspirate was performed.[1,6] For the purpose of uniformity and ease of comparability, clinical staging was done using the SEER (Surveillance, Epidemiology and End Results) clinical staging.[15] In addition; cases of Burkitt's lymphoma were further staged according to the National Cancer Institute (NCI).[16] Staging was done using at least clinical signs and diagnostic imaging (chest radiographs and abdominal ultrasonography), in all patients, and when necessary surgery and cytology. Reporting the results of cancer treatment response was based on World Health Organization guidelines.[17]

Data Analysis and Statistical Techniques.

Data analysis was done using the SPSS version 11.0. Means, medians and standard deviations were computed to summarize continuous variables and proportions and percentages for qualitative variables .The Student's t-test for independent samples was used to investigate the significance of two mean values while the chi-square test was used for the association of two categorical variables. Statistical significance was set at $p<0.05$. Risk factors of early death were analyzed by computing the odds ratio and 95% confidence intervals using involvement of various organs at diagnosis as variables. Statistically significant risk factors were then subjected to logistic regression to determine independent predictors of early death. The outcome variable was coded as either death within 30 days of diagnosis or death beyond 30 days. Cases that were discharged against medical advice in less than 30 days from diagnosis were excluded from the analysis of risk factors for early death. Diagnosis of cancer was made on each child at different points in time during the seven year period. Survival in terms of time between diagnosis and death was analyzed for all patients using the Kaplan-Meier method.[18]

Results

During the study period, 88 cases of childhood cancer were diagnosed at the Department of Paediatrics out of which there were 52 deaths. However, 4 cases of cancer mortality were excluded from the analysis due to lack of completeness of important data.

The ages of all the remaining 84 patients at diagnosis ranged from 1-13 years with a mean of 7.0 ± 3.2 and median of 7.0 years. Among all cancer cases seen, there were 62(73.8%) males and 22(26.2%) females giving a male: female ratio of 2.81: 1.0

The distribution of the different tumour types seen in the 84 cancer patients studied is shown in Table I and reveals that Burkitt's lymphoma constituted the predominant tumour type followed by the leukaemias and Wilm's tumour.

Table I: Distribution of tumor types in all cases of cancer seen in the Department of Paediatrics, UCH, Ibadan, 1998-2004.

Tumour type	Frequency	Percent
Burkett's Lymphoma	43	51.2
Other Non-Hodgkins lymphomas	8	9.5
Leukaemias	10	11.9
Wilm's Tumour	10	11.9
Rhabdomyosarcoma	4	4.8
Neuroblstoma	4	4.8
Hepatoblastoma	2	2.4
Retinoblastoma	1	1.2
Osteosarcoma	1	1.2
Thymoma	1	1.2
Total	**84**	**100.1**

The duration of the illness at presentation in UCH ranged from 1 week to 52 weeks with a mean of 9.83 $\pm$ 9.33 weeks and median of 6 weeks.

Based on SEER stages 8(9.5%) of all cases had localized disease, 16(19.1%) had regionalized disease and 60 (71.4%) had diffuse or metastatic disease at diagnosis. Similarly, among the mortality cases, majority 40(83.3%) presented with metastatic

Introduction

Early deaths (defined as death occurring within 30 days of cancer diagnosis) could be an important indicator of the poor quality of cancer care often attributed to delayed diagnosis, rapid progression of disease or treatment related events such as chemotherapy toxicity and surgical complications.[1-5] However, risk factors for early deaths from childhood cancer have received limited attention in both clinical series and population based studies.

The population-based Childhood Cancer Registry of Piedmont (CCRP) Italy[6] investigated the occurrence of early death in 3006 cases of childhood cancer diagnosed during the period 1967-1998. The proportion of children with cancer who died within 1 month of diagnosis decreased from 10.8% in 1967-1978, to 5.3% in 1979-1988 and 1.8% in 1989-1998. This decreasing trend was attributed to early and improved diagnosis, more effective therapy or more frequent referral to specialized centres. Similarly, Hamre *et al*[1] reported a decrease in the proportion of early deaths associated with childhood cancer during the past 2 decades in the United States. This decreasing trend is adduced to earlier diagnosis or improved imaging capabilities, surgical techniques, medical therapy, and supportive care. Awareness of the need for early diagnosis and referral of childhood cancer with a focus on high-risk groups is therefore important in improving childhood cancer survival. Risk factors for early death observed by various workers include age <1 year, diffuse disease at diagnosis, a diagnosis of acute non-lymphocytic leukaemia, non-Hodgkin lymphoma, neuroblastoma, central nervous system tumour or hepatic tumour.[1,6]

Unfortunately, the matter of early deaths in cancer and its risk factors have received little attention in the developing world and indeed in Nigeria. The few available data on childhood cancer from Nigeria suggest a poor outcome with majority being dead or lost to follow up within a year of diagnosis.[7-9] Identification of risk factors for early deaths and other factors militating against survival from childhood cancer is therefore, important in developing appropriate strategies to improving survival. The objectives of this review were therefore to determine the frequency of early deaths and associated risk factors as well as identifying other challenges to survival in children suffering from cancer.

Methodology

The design was a retrospective study of children with cancer at the Department of Paediatrics of the University College Hospital (UCH) Ibadan, Nigeria. The UCH is an 850-bed tertiary institution located in Oyo state in the South- Western geopolitical zone of Nigeria. It receives referrals primarily from the state and suburbs but occasionally from various states in both the northern and southern parts of the country.

The care of children with cancer in this hospital involves a dedicated paediatric oncology specialist who continues to upgrade his knowledge and care of the patients. Radiotherapy is consistently available but due to high costs, sometimes not affordable by parents. Cytotoxic drugs are usually available for the various cancers seen in the hospital. During the study period Burkitt's lymphoma was treated with modified Ziegler's regimen designated as intravenous (i.v.) cyclophosphamide 1g/m^2 on day 1, i.v. vincristine 1.5mg/m^2 day 1, i.v. methotrexate 37.5mg/m^2 on day 1 or 12.5mg/m^2 given orally on days 1-3 and oral prednisolone 40mg/m^2 in 3 divided doses on days 1-3. Subcutaneous cytosar 100mg/m^2 per day given 12hourly on days 1-3 could be given in place of i.v.methotrexate. Intrathecal cytosar 50mg/m^2 or methotrexate 12.5mg/m^2 on days 1 and 5 were also given and the entire cycle repeated every 14 days up to a total of six cycles. Other Non-Hodgkin's lymphomas were treated with eight courses of standard 21day-CHOP regimen including cyclophosphamide 750mg/m^2 i.v on day 1, doxorubicin 50mg/m^2 i.v. on day 1, vincristine 1.4mg/m^2 on day 1 and prednisolone 100mg daily for 5days. The COAP regimen used for remission induction and consolidation of Acute lymphoblastic leukaemia consisted of i.v. cyclophosphamide, vincristine, subcutaneous cytosine arabinoside and oral prednisolone in a 28 day cycle.[10] Intrathecal cytosine arabinoside was also given as central nervous system prophylaxis. Following complete remission, maintenance therapy consisted of oral methotrexate and 6-mercaptopurine. Acute myeloid leukemia (AML) was treated with doxorubicin, cytosine arabinoside and 6-thioguanine (DAT). However, due to the high cost and frequent unavailability of 6-thioguanine, COAP was more often used for the treatment of AML. Wilm's tumour chemotherapy was based on the conclusions of the National Wilms' Tumour Study program using various combinations of Vincristine, Actinomycin D, Doxorubicin and cyclophosphamide.[11] Patients with rhabdomyosarcoma were treated based on the recommendations of the Intergroup Rhabdomyosarcoma Study IV (IRS IV) with combinations of cyclophosphamide, actinomycin D and cyclophosphamide (VAC) and radiotherapy.[12] One patient with hepatoblastoma was discharged against medical advice without treatment whilst the second with hepatoblastoma as well as the only patient with osteosarcoma were very ill at presentation and died before treatment could be started. The patient with retinoblastoma had localized disease and was treated with surgery and radiotherapy. The patients with Neuroblastoma were treated with the Dana-Farber Cancer Institute MADDOC protocol[13] consisting of the use of Nitrogen Mustard, Adriamycin, DTIC, Cisplatin, Vincristin and cyclophosphamide but with exception that DTIC was omitted due to its non-availability.

disease, 6(12.5%) presented with regionalized disease and only 2 (4.2%) had localized disease at diagnosis.

The outcome of all the patients studied is shown in Table II. Majority (57.1%) of the cases died while the remaining 42.9 % were lost to follow up at varying times ranging from before commencement of treatment to after completion of treatment. The main reason for default was discharge against medical advice due to financial difficulty followed by failure to return for treatment when allowed home on parole between courses of treatment.

Tabke II: Outcome of 84 children with cancer.

Outcome	No.	Percent
Died	48	57.1
Default after completion of treatment	3	3.6
Discharged on parole between Treatment courses and defaulted	13	15.5
Discharged against medical advice for financial difficulty	14	16.7
Discharged against medical advice due to poor response	4	4.8
Referred abroad for continuation of therapy	2	2.4
Total	**84**	**100.1**

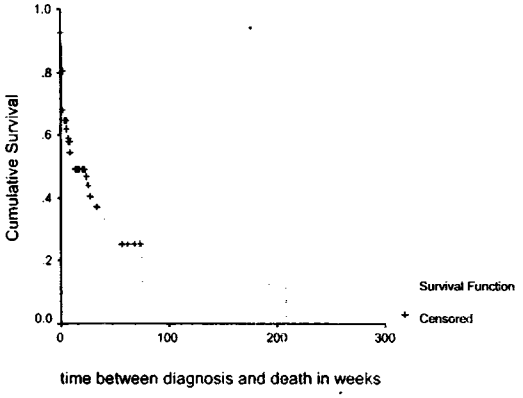
Out of all the cases, 64(76.2%) received treatment but only 11(13.2%) of all cases completed the required courses of treatment. Treatment consisted of surgery and chemotherapy in 1(1.6%), chemotherapy and radiotherapy in 2 (3.1%), chemotherapy and surgery in 5 (7.8%) and chemotherapy alone in 56 (87.5%) of the treated children. Analysis of state of response when last seen showed that among 64 children that were treated, 15(23.4%) had complete response out of which 12(18.8%) later had relapse whereas 20(31.3%) had partial response out of which 2 (3.1%) later had disease progression. There was no response in 9(14.1%), disease progression in 5 (7.8%) and response could not be assessed in the remaining 15(23.4%) patients because they either died or were discharged before four weeks of treatment. Among the 11 patients who completed their required courses of treatment 6 had initial complete response with relapse later, 3 had partial response, 1 had partial response with disease progression later and 1 had disease progression in spite of treatment but second line drugs could not be obtained locally.

Out of the 43 cases with Burkitt's lymphoma, only 36 received chemotherapy and the remaining 7 either died before treatment could be commenced or were discharged from the hospital against medical advice. However, only 26 could be assessed for response to treatment as 10 patients died early and so response could not be evaluated. Six (23.1%) of the 26 evaluable patients had complete response, 17 (65.4%) had partial response and 3(11.5%) had no response. Twelve (70.6%) of the 17 patients with partial response had incomplete treatment due to financial constraints and defaulted from treatment.

Cancer Survival.

Survival from diagnosis to death ranged from 1 day to 208 weeks with a mean of 45.01 weeks and a standard error of 14.82 weeks. Median survival was 10 weeks and the 26 week (6 month) survival estimate was 0.41 (Figure I).

Figure I: Survival function of all cases of cancer.



At one year from diagnosis, cumulative survival was about 25%. There was no significant correlation between duration of illness at presentation in UCH and survival (ℓ= 0.032, p=0.831) among mortality cases.

Early Deaths.

Out of the 84 cases analyzed there were 29 early deaths yielding an early death rate of 34.5 %. Five patients were discharged against medical advice in less than 30 days from diagnosis and so were excluded from the analysis of risk factors of early death.

Table III shows the frequency of early death in different tumours and reveals that neuroblastoma and hepatoblastoma had higher frequencies of early death than others. Logistic regression analysis of all the underlying causes of death (tumours) however showed that none was a significant predictor of early death. Analysis of age groups (<1 year, 1-4, 5-9 and 10-14 years) also showed no significant association between age group at diagnosis and early death.

Table III: Frequency of early deaths in different tumours.

Tumour type	All cases†	Early deaths No.	%
Burkitt's lymphoma	39	15	38.5
Other Non-Hodgkin's lymphomas	8	2	25.0
Leukaemias	9	4	44.4
Wilm' tumor	10	3	30.0
Rhabdomyosarcoma	4	1	25.0
Neuroblastoma	3	2	66.7
Hepatoblastoma	2	1	50.0
Retinoblasma	1	0	0.0
Osteosarcoma	1	1	100
Thymoma	1	0	0.0

†Excluding those discharged against medical advice within 30 days.

Risks factors for early death were assessed based on clinical stage (metastasis versus non-metastasis) and organ involvement at diagnosis and the results shown in Table IV.

Table IV: Stage and Organ involvement as risk factors for early death.

Risk factor	Early death (n=29)	Survival beyond 30 days (n=49)	All cases (n=78)	OR (95% CI)
Stage				
Metastasis	27	27	54	11.00(2.35, 51.45)*
Organs				
CNS†	8	12	20	1.18 (0.41, 3.33)
Lungs	8	4	12	4.29(1.16, 15.84)*
Live enlargement	17	22	39	1.74(0.69, 4.40)
Liver masses	10	5	15	4.63(1.39, 15.39)*
Splenic Enlargement	14	18	32	1.61(0.63, 4.08)
Intra-splenic Masses	5	1	6	10.0(1.11, 90.45)*
1 kidney	7	11	18	1.10(0.37, 3.25)
Both kidneys	7	3	10	4.88(1.15,20.69)*
Testis	2	2	4	1.74(0.23, 13.07)
Ovaries	0	1	1	-

The risk of early death was increased in the presence of metastasis, involvement of the lungs and bilateral kidney involvement. Enlargement of the liver and spleen were associated with increased risk of early death only when there was gross radiological evidence of masses or infiltrates in them. Logistic regression analysis of organ involvement showed only pulmonary involvement to be a statistically significant independent predictor of early death (exp β= 4.45 [95% CI = 1.07, 18.53]). Ovarian involvement was bilateral, occurred in only one patient and survival was beyond 30 days. Only one patient had bilateral testicular involvement and died early. Fifteen (51.7%) of the 29 cases of early death received no treatment before death either because they came in very sick and were being resuscitated or could not raise enough funds to start treatment early enough.

Analysis of the rate of early death in patients with the different NCI stages of Burkitt's lymphoma revealed that Stage D disease accounted for the majority of cases and was associated with increased risk of early death (Table V). Although the early death rate among all the patients with Burkitt's lymphoma was 38.5 per cent, among the 36 patients who received treatment, 10 died early yielding an early death rate of 27.8 per cent.

Table V: Early deaths in different stages of Burkitt's Lymphoma.

Stage	All cases	Early deaths No.	%	χ^2	p value
A	2	0	0	-	-
B	3	0	0	-	-
C	12	3	25.0	0.63	0.426
D	22	12	54.5	4.07	0.044

Discussion

The 34.5% rate of early deaths observed in this study is much higher than the rates reported by other workers that have ranged from 4.1% to 10.8 %.[6, 19, 20] It is however important to note that the latter reports are based on population-based cancer registries and therefore involved larger numbers of children registered over time periods sometimes up to three decades.[6] Never- the- less the high early death rate observed in the present study is a cause for concern. Among the factors that might be responsible for the frequency of early deaths is presentation at a metastatic stage of the disease which was observed in over seventy percent of all cases and eighty per cent of all deaths in the present study. The increased risk of early death in patients with metastatic disease at diagnosis observed in our study has been previously reported by other workers.[6] However; duration of illness at presentation did not significantly predict early deaths. This may be because although generally speaking the longer the delay in the duration of the illness, the more advanced the disease, Burkitt's lymphoma which contributed most to early deaths in our study is a rapidly proliferating tumor.[21] It may therefore present as an advanced tumour within a very short time.

Presentation at stage D of Burkitt's lymphoma was also associated with an increased risk of early death in our study. This is in keeping with findings by Olweny *et al*[22] in Uganda where 88 percent of early deaths in Burkitt's lymphoma were patients in stages C and D.

Unfortunately, over half of our cases presented in stage D which is in consonance with recent findings by Fasola *et al*[23] who observed 76.1% of Burkitt's lymphoma patients studied in Ibadan to be in stage D. The frequency of non-response in our patients with Burkitt's lymphoma was 11.5 % and similar to 11 % observed in Uganda. However, the rate of complete response in our patients was 23.1% and although similar to earlier findings in our institution of 22.8 %,

it was low compared to 81 % observed in Uganda.[22] The early death rate observed in our study was also high compared with 33 out of 280 patients (11.8%) in the report from Uganda. The superior response achieved in the Ugandan children compared to ours was probably due to the fact that while the studies reported by Olweny *et al*[22] were all Clinical Trials in which patients would have had ready access to adequate chemotherapy and supportive care unlike our patients who were financed by their parents majority of whom could not afford the cost of drugs. Hence most of the patients who had partial response were unable to complete the course of chemotherapy required to achieve complete response. This accounts for the disparity in complete response rates in spite of the similar non-response rates of patients in our study and those reported by Olweny *et al.*[22]

Lack of treatment also appreciably contributed to early deaths in our study. Over 50% of the cases who died early received no treatment because they were very ill and were still being resuscitated and prepared for treatment when they died. These problems were probably due to late diagnosis and referral from primary and secondary health facilities to tertiary centres for treatment.

Previous studies have observed increased risk of early deaths in certain tumours compared to others. These include a diagnosis of neuroblastoma, central nervous system tumour, acute non-lymphocytic leukaemia and tumours in the liver.[1,6] Our study similarly found higher early death rates in neuroblastoma and hepatoblastoma compared with other tumours. However, logistic regression analysis of the tumours in the present study failed to reveal increased risk in any of them probably due to the small numbers of cases of neuroblastoma and hepatoblastoma involved. An increased risk of death in infants with cancer has also been observed but no infants were seen in the present study and logistic regression analysis failed to reveal any age group to be at increased risk of early death.

In the present study, the odds for early death were increased in the presence of intra-hepatic masses. Other workers have similarly observed that children with liver tumours are at increased risk of early death.[1,6] Other factors found to be associated with increased risk of early death in our study include splenic masses, pulmonary metastasis and involvement of both kidneys by the tumour. It is note worthy however that clinical enlargement of the liver and spleen without discrete masses or infiltrates within the respective organ was not associated with early death. Logistic regression showed only pulmonary metastasis to be a significant independent predictor of early death. . In view of these findings, management of patients with tumour involvement of the lungs, both kidneys and tumour infiltration of the liver and spleen should include careful monitoring if possible in an intensive care unit to prevent early death.

Central nervous system disease was found not to be significantly associated with early death in this study unlike what was reported by Pastore *et al*,[6] Hamre *et al*[1] and Creutzig *et al.*[24] The difference in the findings between the latter studies and the present one may be due to differences in tumour types prevailing in the different environments involved. While Hamre and Pastore studied children in Italy and Hamre in the United States where primary central nervous system tumours are quite common and associated with a high risk of early death, the patients in the present study where mainly cases of Burkitt's lymphoma with involvement of the central nervous system It is therefore probable that primary central nervous system tumours are more aggressive than Burkitt's lymphoma in causing early mortality.

The findings of the present study suggest poor survival from cancer although the results were however limited by a high rate of loss to follow up and incomplete treatment. It is however of interest to observe that the obtained values are in keeping with previous reports of poor survival from childhood cancers in Nigeria. Recently, Kagu *et al* [25] reported a mean survival of 10.5 $\pm$ 3.4 weeks in children who died of Burkitt's lymphoma and a 5-year survival of only 1.9%. Other previous reports from Nigeria have also revealed a poor outcome with death of most of the children in less than a year of diagnosis.[7-9] These studies have however been characterized by high rates of default and such cases often assumed to have died. This actually makes it difficult to obtain the accurate survival rates in Nigeria. The present study is similarly limited by the fact that it is based on hospital records and almost 43% of the patients defaulted from treatment mainly due to financial constraints. Another major reason for default was the opportunity of going home on parole following some response to treatment and this poses a major challenge bearing in mind the often protracted duration of cancer treatment making it unrealistic for a child to remain on admission throughout the length of therapy. An interplay of the latter two factors resulted in the poor response to therapy observed in our study.

The matter of discharge against medical advice observed in the present study is a major challenge in management of childhood cancer in Nigeria and has been previously reported by Fasola *et al*[23] in Ibadan. Our study has shown that in addition to financial difficulty being the major reason as reported by Fasola *et al*[23], some other parents ask for discharge of their children due to poor response to first line therapy making them to resort to alternate therapy by traditional healers. In addition to efforts at correcting this attitude which is due to ignorance, there is also need to make concerted efforts to provide second line cytotoxic drugs which are usually hard to find in the country and occasionally have to be ordered from abroad by a few wealthy parents.

Conclusion

This study has shown that survival from childhood cancer at the Paediatrics Department of the University College Hospital Ibadan for the period under review was poor with a zero 5-year survivor; the median survival was10 weeks and the patient who lived longest died 208 weeks (4 years) after diagnosis. Most patients presented with advanced disease with a resultant high rate of early death often before or shortly after commencement of treatment. Risk factors for early death include the presence of intra-hepatic masses, intra-splenic masses, and bilateral kidney involvement by tumour and pulmonary metastasis the latter being an independent predictor of early death. Other challenges to survival include a high rate of loss to follow up, discharge from treatment against medical advice and financial constraints to completion of therapy. Health education of the public and sensitization of medical practitioners on the need for early presentation at the hospital, prompt referral as well as free or significantly subsidized treatment for cancer could have a significant impact on childhood cancer survival in Nigeria. Careful evaluation of all children with cancer to identify risk factors for early death utilizing routine chest X-rays and abdominal ultrasound scans among other measures and prompt anticipatory management may also reduce the frequency of early deaths and improve survival. Population-based cancer registries should be established across the country to in addition to keeping record of all cancer cases also monitor and record survival and deaths in order to accurately quantify the incidence and survival of childhood cancer.

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