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Original Paper

The Tygerberg Hospital Children's Tumour Registry 1983–1993

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This study records the disease profile and outcome of all 492 children with confirmed cancer below the age of 15 who were admitted to Tygerberg Hospital, South Africa, from 1983 to 1993. The black (48.3%), so-called coloured (30.3%) and caucasian (21.3%) children did not represent a confined geographical area. Leukaemia (22.8%), brain tumours (20.5%), lymphomas (15.2%), nephroblastomas (10%), neuroblastomas (8.5%) and retinoblastomas (5.7%) were the most common tumours. All children were treated with standard protocols and included in the Kaplan–Meier survival analyses. 14 patients were lost to follow-up. Projected survival in (acute lymphoblastic leukaemia) ALL was 63% in white children, but only 17% in black children. Survival was 65% in stage 1 and 2 Wilms' tumour, and exceeded 50% in medulloblastoma and astrocytoma. So-called African Burkitt's lymphoma occurred in all population groups. Overall, 5-year survival in Hodgkin's disease was 70%. Black and coloured children with neuroblastoma presented mainly with stage 3 and 4 disease. All 26 black and coloured children with retinoblastoma had a negative family history and advanced disease which needed enucleation.

Key words: cancer, children, hospital registry, distribution, survival, ethnic, Africa
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INTRODUCTION

THE TYGERBERG Hospital Children's Tumour Registry (TBHCTR) is a hospital-based tumour registry (HBTR) which was established in March 1983. Tygerberg Hospital (TBH) lies within the metropole of Cape Town in the Western Cape region of the Republic of South Africa (RSA), and serves as the academic hospital for the University of Stellenbosch. The paediatric oncology unit at TBH is one of two units in the Western Cape region which in 1994 had an estimated 3 620 150 inhabitants [1]. Some children from the Eastern Cape and Northern Cape provinces and the majority of children with cancer in Namibia were also referred to this centre. Treatment facilities in Namibia were improved in 1989 and, after this date, patients were mainly referred for radiotherapy to TBH. Although HBTRs have limitations with regard to the epidemiological information which they can generate, they may provide knowledge about the spectrum of pathology encountered and the outcome of treatment; contribute data to regional and national registries; and establish a factual base for appropriate teaching, research and planning of health services.

The absence of a formal paediatric registry in the RSA, the paucity of epidemiological data from Africa as a whole, and the need to objectively quantify the end result of the increasingly intensive and expensive therapy in a mainly socio-economically disadvantaged population provided the incentive to initiate this HBTR. The main objectives of this report are to review the disease profile and outcome of treatment in the 10 year period starting in March 1983, and to discuss other positive contributions to paediatric oncology that have emanated from this registry.

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MATERIALS AND METHODS

All children below 15 years of age who presented at TBH with a confirmed malignant disease, intracranial tumour or Langerhans cell histiocytosis were entered in the registry and included in all the analyses. Every new patient's diagnosis was reviewed at a monthly registry meeting. The ICD-O code was used to index the pathology, and diseases were classified as proposed by Birch and Marsden [2, 3]. Copies of pathology slides and other critical diagnostic investigations at the time of diagnosis were filed in the registry. The diagnosis date for new patients is the date on which the investigation which confirmed the diagnosis was performed. The registration date is the date on which the pathological diagnosis was reviewed and accepted as the final diagnosis at the abovementioned registry meeting. The incidence date is the date on which symptoms or signs which could definitely be linked to the subsequent diagnosis of a malignant disease became apparent for the first time. The date

of birth or the estimated age, sex, residential address and ethnic origin were recorded for epidemiological purposes.

Patients were investigated, staged and treated according to internationally accepted protocols with surgery, chemotherapy and radiotherapy used alone or in combination. Treatment protocols primarily used for the more common malignancies include the BFM protocols for acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) [4, 5], CLVPP with low dose involved field radiotherapy in Hodgkin's disease (HD) [6], LSA2-L2 in lymphoblastic lymphoma [7] and COMP in B-cell and other non Hodgkin's lymphomas [7], surgery and radiotherapy for brain tumours, NWTS 3 [8] and later SIOP 9 in Wilms' tumour [9] and a St Jude protocol in neuroblastoma [10]. During this 10 year period, all the necessary investigations and therapeutic modalities were available and provided to all the patients, irrespective of their socio-economic status. The authors have been responsible for the medical and supportive treatment of almost all the children in this registry. The paediatric service at TBH routinely only treats children up to the age of 13 years. A few patients in this registry were therefore managed by adult physicians.

The response to treatment, complications of treatment, compliance with protocols and the short and long term follow-up findings are continuously recorded in a computerised database by a registry clerk, who is a registered nurse. She is assisted by a part time medical officer. Social workers, health professionals in the patient's home environment, parent's employers, school teachers and voluntary organisations are involved from the time of diagnosis to facilitate treatment and long term follow-up. Funding for the registry was obtained through research grants.

Kaplan–Meier analyses for survival and disease-free survival were performed for the major disease categories in March 1993, 10 years after the start of the registry. The date of first admission to TBH and not the incidence date (which may have been earlier) was used for analyses. All patients, including those who had received none or very little specific therapy, were included in the analyses. Children in whom the outcome was unknown at the time of analysis, were censored. All patients were also registered with the national SA Children's Tumour Registry since 1987.

RESULTS

General characteristics of patients registered

The number of tumours in each diagnostic group and the relative frequency of each are indicated in Table 1. The relative frequency of tumours entered in the South African Children's Tumour Registry from 1987 to 1993 are included in this table as a matter of interest [11].

This HBTR includes patients from Namibia, and is therefore not representative of a confined geographical region or population. Of 492 patients, 238 were of mixed ethnic ancestry (so-called coloured population), 149 were black and 105 were caucasian patients. This allowed a comparison of stage at presentation and outcome between ethnic groups in the more common disease categories. Twelve children with Langerhans cell disease were registered in addition to the 492 patients in Table 1. The disease status at the end of the 10 year period was unknown in 14 (2.8%) of the children who had been registered. There were 33 children (12 males, 21 females) below the age of 1 year, 184 children (91 males, 93 females) aged 1–4 years, 132 children (78 males, 54 females) aged 5–9 years and 143 children (90 males, 53 females) aged 10–15 years.

Outcome in major disease categories

The projected survival for the major disease categories is illustrated in Figures 1 to 8. There was a significant (Chi square $P < 0.01$) difference between the 63% 5 year survival rate for ALL in caucasian children and the 17% survival rate in black children (Figure 1). All these children were treated with the BFM ALL 1983 medium risk protocol by the investigators. This ethnic difference in survival could not be explained by differences in treatment compliance, and the following risk factors for ALL did not differ in the two groups: white cell count $> 20 \times 10^9$/l at diagnosis, hepatomegaly > 5 cm, male sex, age < 2 years or > 10 years, prominent mediastinal lymphadenopathy, platelet count $< 50 \times 10^9$/l.

The survival probability in AML was 15% (Figure 2). Six children are currently off treatment and in continuous remission at 24, 32, 40, 40, 49 and 54 months, respectively, since diagnosis.

Table 1. Distribution of patients in main diagnostic groups

Diagnostic Group	*n*	Male	Female	Black	Coloured	Caucasian	Relative frequency (%) TBHCTR* 1983–1993	Relative frequency (%) RSA† 1987–1993
Leukaemia	112	56	56	21	52	39	22.8	23.0
Lymphoma	75	51	24	13	45	17	15.2	12.0
CNS and intracranial	101	57	44	34	48	19	20.5	13.0
Sympathetic nervous system	42	20	22	15	16	11	8.5	8.0
Retinoblastoma	28	11	17	17	9	2	5.7	5.0
Renal	49	23	26	19	24	6	10.0	16.0
Hepatic	8	7	1	2	4	2	1.6	2.0
Bone tumours	19	11	8	2	13	4	3.9	3.0
Soft tissue sarcoma	23	9	14	10	11	2	4.7	9.0
Germ cell tumours	17	5	12	4	11	2	3.5	4.0
Carcinoma	14	9	5	8	5	1	2.8	–
Other	4	2	2	4	0	0	0.8	5.0
Total	492	261	231	149	238	105	100.0	100.0

* TBHCTR, Tygerberg Hospital Children's Tumour Registry; † RSA, Republic of South Africa.

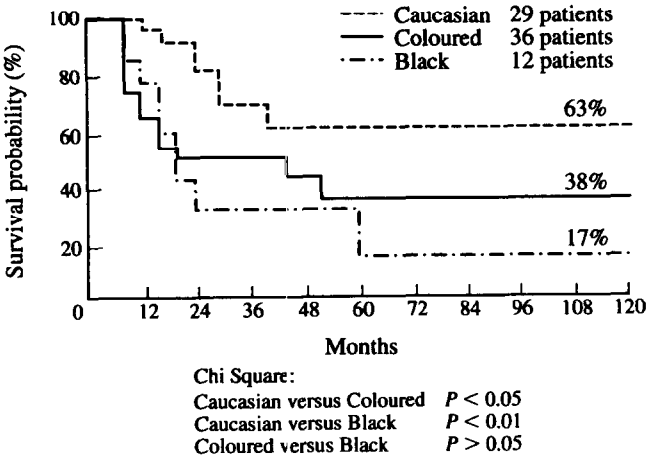

Figure 1. Leukaemia (ALL) 1983–1993: survival probability.

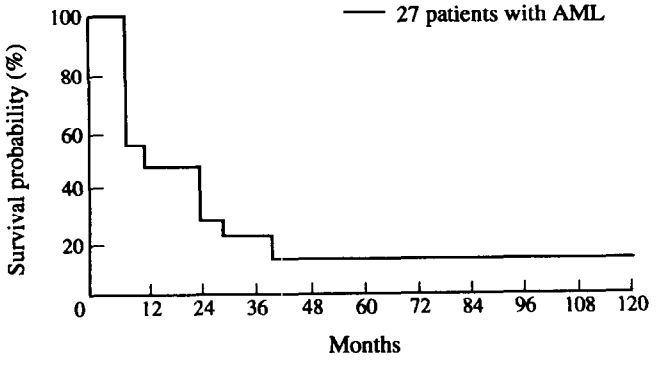

Figure 2. Leukaemia (AML) 1983–1993: survival probability.

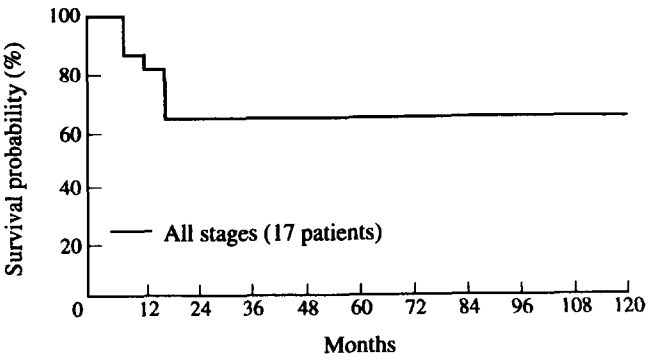

Figure 4. Lymphoma (Non-Hodgkin's) 1983–1992: survival probability.

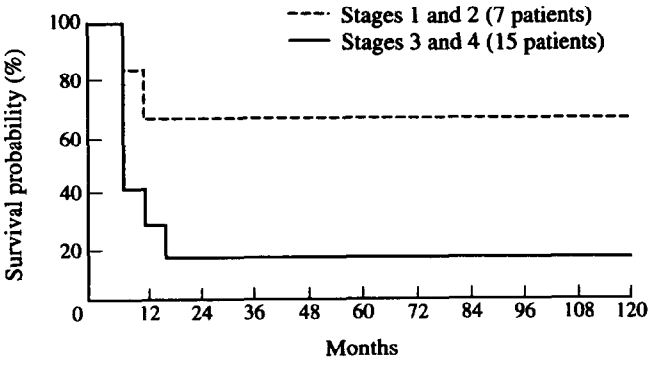

Figure 5. Lymphoma: Burkitt/B cell 1983–1993: survival probability.

The survivors include 3 of 8 coloured, 2 of 5 white and 1 of 3 black children.

The 5 year survival rate in HD for all patients was 70% (Figure 3). Disease-free survival at 5 years was, however, much lower at 35% (not illustrated) and recurrences occurred up to 80 months after diagnosis. The 17 patients with lymphoblastic lymphoma had 65% survival rate. No deaths or recurrences occurred later than 18 months after diagnosis (Figure 4). The survival in 22 B-cell lymphoma patients, all treated with COMP, was 60% in stage 1 and 2 disease, and 15% in stage 3 and 4 disease (Figure 5). Typical so-called African Burkitt's disease patients presenting with swelling of the jaw, was seen in 2 of 5 caucasian patients, 3 of 12 coloured patients and 2 of 5 black patients. Abdominal disease was the presenting feature in 14 children, while one child presented with a mediastinal mass. Involvement of the central nervous system at diagnosis was present in 3 black patients. All relapses occurred within 8 months of diagnosis and all death occurred within 16 months of diagnosis.

Over 50% of children with medulloblastoma and astrocytoma, but only 10% of cases with brain stem glioma, survived 5 years (Figure 6). All these patients were treated with surgery and/or radiotherapy only. The sequelae of the disease and/or therapy have not yet been fully analysed. We are at present engaged in follow-up and evaluation of all long term (more than 5 years) survivors of paediatric cancer.

In neuroblastoma, the projected 5 year survival was 100% in Evans stage 1 and 2 disease, 50% in stage 3 and 15% in stage 4

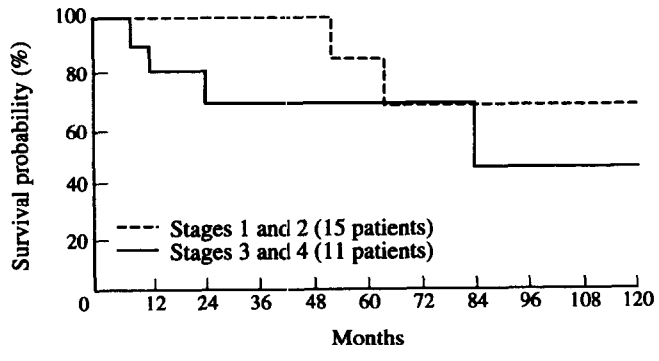

Figure 3. Lymphoma (Hodgkin's) 1983–1993: survival probability.

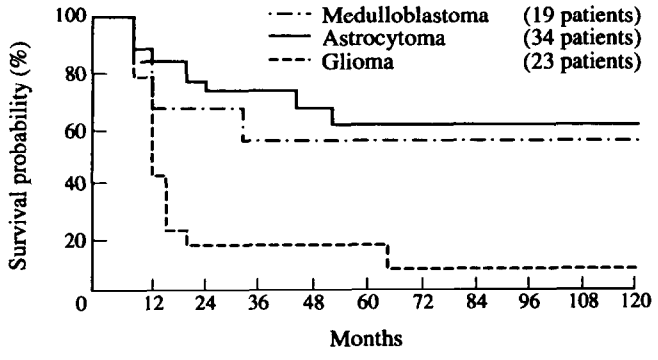

Figure 6. Medulloblastoma/astrocytoma/glioma 1983–1993: survival probability.

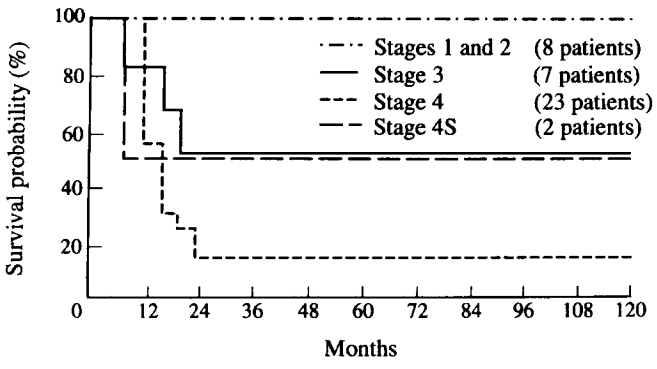

Figure 7. Neuroblastoma 1983–1993: survival probability.

disease (Figure 7). One of 2 patients with stage 4S disease is a long term survivor. All patients received chemotherapy and resection of primary or residual disease when possible. Evans stage 3 or 4 disease was present in 33% of caucasian children, 86% of coloured children and 100% of black children on admission to TBH.

All 27 patients with retinoblastoma presented with stage III or stage IV disease and needed an enucleation. The survival rate was 52%. No family history of retinoblastoma was obtained in any patient.

The survival in stage 1 and 2 Wilms' tumour was 65% and almost 40% for stage 3, 4 and 5 combined (Figure 8). The latest recorded relapse occurred 56 months after diagnosis. There was no difference between the ethnic groups, both with regard to stage at presentation or survival.

Amongst 15 patients with osteosarcoma, 10 died of disease, 2 were lost to follow-up and 3 children are disease-free at 3, 8 and 10 years, respectively. The survival time and disease-free survival at 5 years in rhabdomyosarcoma was 30%. The last 3 children, who presented with hepatoblastoma or hepatocellular carcinoma, were treated according to a SIOP protocol with doxorubicin and cisplatinum followed by a total resection. 2 of these children, one with hepatoblastoma and the other with hepatic carcinoma, are alive and disease free more than 2 years after diagnosis. The third child died of recurrence of liver carcinoma.

DISCUSSION

During the 10 years of the registry, there were many advances both in specific and in supportive therapy. Patients treated during the early part of this study did not benefit from these advances. This, and the fact that all the patients recorded by the TBHCTR were included in the Kaplan–Meier analyses, irrespective of the treatment received, influenced the survival rates. The registry does, however, provide accurate information on disease presentation and outcome in different population groups over a 10 year period. It needs to be clearly stated, however, that the small numbers in many of the subgroups are associated with very large confidence intervals, and that the calculated survival rates should be interpreted accordingly. Poor follow-up often prevents the calculation of accurate survival figures in developing countries. In this series, the loss of only 3% of patients to follow-up contributes to the reliability of the results.

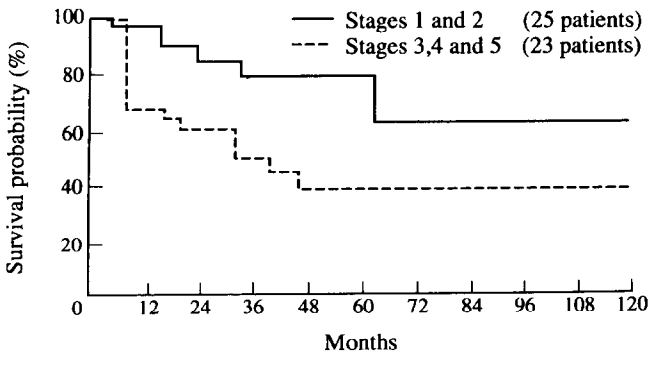

Figure 8. Nephroblastoma 1983–1993: survival probability.

The survival of 14 black children treated for ALL from 1977 to 1988 was 21% compared to 60% in 20 caucasian children treated during the same period. The median survival was 9 months in black and 52.5 months in caucasian children [12]. The biological reason for the difference in outcome between caucasian and black children has been investigated but is not clear [13]. ALL in black African children is a high risk disease and must be treated accordingly. A change in the treatment protocol has been implemented for these children. The 5 year survival of 70% in Hodgkin's disease is followed by late relapses. MOPP and ABVD, alone or in combination were used as salvage therapy [14, 15]. Poor outcome in stage 1 and 2 disease is of particular concern because it is not a consequence of understaging or poor compliance with treatment. The CLVPP protocol was first used in the U.K., and is similar to MOPP except that mustine is replaced with chlorambucil, which causes much less nausea. This protocol has, however, not been compared with MOPP or ABVD in a double-blind trial. Because of the late relapses in our patients, we are now using ABVD as first line chemotherapy in Hodgkin's disease. The results of treatment in early and advanced B-cell NHL are inferior to published results. Since 1993, all new patients are treated according to the LMB 89 protocol and the short term result appears favourable. Although the outcome in Wilms' tumour in patients who were treated with NWTS protocols was reasonable, many patients present with very large tumours, which are technically difficult to resect. The tumour stage may be upstaged as a result of incomplete resection or rupture during surgery, which necessitates more intensive therapy and affects the prognosis adversely. This influenced us in 1990 to change to the SIOP protocol, which contains preoperative chemotherapy. Although the reported long term outcome with the NWTS and SIOP protocols is similar, we are of opinion that the morbidity of treatment is less with the SIOP protocol in a developing country. The poor outcome in especially brain stem gliomas, and the known high morbidity of radiotherapy to the brain in young children, induced us, in 1993, to add adjuvant chemotherapy to the treatment of children with brain tumours, which are potentially chemotherapy sensitive.

The incidence of different cancers cannot be reliably derived from a hospital-based registry, which does not register all the patients in a particular geographical area. All eight paediatric cancer units in the RSA have registered their patients at the national SA Children's Tumour Registry since 1987. The relative frequency of tumours for the period 1987–1993 was reported at the first continental meeting of the International Society of Paediatric Oncology (SIOP) in Africa in 1994. An overall annual incidence of only 76 new cases per million children suggests that these data are incomplete. The relative frequency of tumours in the TBHCTR is, however, very similar to those in the national South Africa Children's Cancer Registry, with the exception of brain tumours, which are known to be under-reported in the national registry, and Wilms' tumour and soft tissue sarcomas,

which have a higher national relative frequency. The relative frequency of tumours in the TBHCTR resembles that of western registries. The predominance of Burkitt's lymphoma, relative high incidence of AML, rarity of neuroblastoma, low incidence of brain tumours and the presence of Kaposi sarcoma, which are typical of Central Africa, are notably absent in the TBHCTR [16–18].

The occurrence of so-called African and North American Burkitt's lymphoma in both our black and caucasian patients is interesting. We have not examined the chromosomal abnormalities in these tumours. Although no HIV-related cancers were seen, the estimated 9.62% prevalence rate of HIV infection in women attending antenatal clinics during 1993 in the Natal/KwaZulu region of the RSA, will probably be reflected in the appearance of AIDS-related cancers in childhood in this country in the future [19]. The marked discrepancy in stage at presentation in neuroblastoma between white children on the one hand and coloured and black children on the other hand, may reflect a delay in diagnosis. 14 black patients were referred from Namibia. The time required to move down the referral chain from a primary health care facility in rural Namibia, to the treatment centre in South Africa, may have contributed to the presence of advanced disease in patients at the time of registration. A poor understanding of disease and poorer accessibility to health services in the coloured and black population in South Africa may also have contributed to delayed diagnosis. Differences in biological behaviour of neuroblastoma in caucasian and black children which could explain this difference, have not been recorded, and can therefore not be considered as a likely explanation. The (8%) relative frequency of neuroblastoma is higher than recorded elsewhere in Africa. The relative high incidencec of retinoblastoma is in keeping with other countries in Africa. The very high incidence of sporadic retinoblastoma warrants comment and needs to be confirmed in future with more detailed family histories.

The prospective collection of data for this registry has forced members of staff to pay more attention to essential detail of diagnosis, treatment and follow-up. This in itself has contributed to improvement in the quality of care of our patients. The information generated by the registry has been successfully applied to convince faculty members, health administrators and the public of the need for and merits of cancer therapy in children, and has enabled the establishment of an effective paediatric oncology unit at this university hospital. The main expense to maintain the registry is the salary of a registry clerk which, in the TBHCTR, has been the equivalent to the remuneration of trained nurse working half days. This annual expense is less than the cost of drugs required to treat one child with a modern chemotherapy regimen. The benefits of a registry thus clearly outweigh the cost. Teaching for under- and post-graduate students has benefited in that appropriate information about disease patterns and response to treatment in the local population have been provided. The registry forms a usefully databank for retrospective research projects, and has facilitated scientific cooperation with other institutions. This hospital based registry has provided an accurate audit of the paediatric cancer service at Tygerberg Hospital.

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