

**Article type:**

Original article

**Title:**

Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials

**Authors:**

C. A. Stiller, M. E. Kroll, K. Pritchard-Jones

**Affiliations:**

Childhood Cancer Research Group, Department of Paediatrics, University of Oxford, Oxford, UK (CAS, MEK)

Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (MEK)

Department of Paediatric Oncology, Institute of Child Health, University College London, Great Ormond Street Hospital for Children NHS Trust, London, UK (KPJ)

**Address for correspondence:**

Mr C. A. Stiller

Childhood Cancer Research Group

Department of Paediatrics

New Richards Building

University of Oxford

Old Road Campus

Oxford OX3 7LG

UK

Telephone +44 1865 617802

Fax +44 1865 617801

E-mail [charles.stiller@ccrg.ox.ac.uk](mailto:charles.stiller@ccrg.ox.ac.uk)

# **Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials**

CA Stiller, ME Kroll, K Pritchard-Jones

## Abstract

### *Background*

Inclusion in clinical trials is generally viewed as best practice for most newly diagnosed childhood cancers, but the impact on population-based survival has rarely been examined.

### *Patients and Methods*

Population-based data were analysed for 25,853 children (66% of all registered childhood cancers) diagnosed in Britain during 1978-2005 with acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), Hodgkin lymphoma, non-Hodgkin lymphoma, medulloblastoma, neuroblastoma, Wilms tumour, hepatoblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma and germ-cell tumours. Kaplan-Meier survival curves were compared by log-rank tests. Time trends were analysed by Cox regression.

Separate analyses were done for children with ALL, medulloblastoma and neuroblastoma according to clinically relevant age thresholds.

### *Results*

Survival increased significantly during 1978-2005 for every diagnostic category; annual reduction in risk of death ranged from 2.7% (rhabdomyosarcoma) to 12.0% (gonadal germ-cell tumours). Survival increased steadily between trial eras for ALL (age 1-14) and neuroblastoma (age 1-14), but changed little since the mid 1980s for medulloblastoma (age 0-2), osteosarcoma or Ewing sarcoma.

### *Conclusions*

Changes in survival between trial eras parallel those reported by the relevant clinical trials. The increasing level of participation in trials, facilitated by the organisation of specialist care, has underpinned the substantial improvements in survival seen at the population level.

### *Key words*

Cancer registry, childhood cancer, clinical trials, population-based, survival, trends

## Introduction

Survival from childhood cancer has increased dramatically during past decades. In Great Britain, five-year survival rose from 28% for children diagnosed during 1966-1970 to 77% for those diagnosed during 1996-2000<sup>1</sup>. Multicentre clinical trials for childhood acute lymphoblastic leukaemia (ALL) were well established in Britain by 1971<sup>2;3</sup>. At this time, some children with acute myeloid leukaemia (AML) or Hodgkin lymphoma were entered into trials in which most patients were adults<sup>4;5</sup>, but Wilms tumour was the only solid tumour of childhood for which a multicentre trial was open<sup>6</sup>. In 1977, the UK Children's Cancer Study Group (UKCCSG) was formed, one of its principal aims being to develop and participate in a comprehensive portfolio of national and international trials that included the majority of childhood solid tumours and lymphomas<sup>7</sup>. The first UKCCSG trials, for non-Hodgkin lymphoma (NHL), opened in the same year<sup>8;9</sup>. Since then, a succession of trials has been available to patients with almost all the major types of childhood cancer. Results of most of these trials have been reported.

Trends in childhood cancer survival have often been discussed in relation to therapeutic developments in the UK<sup>1;10-13</sup> and elsewhere<sup>14;15</sup>. Hitherto, however, only one study (of ALL) has examined population-based survival according to the exact periods of currency of widely-used treatment protocols<sup>16</sup>. The aim of the present study is to document and interpret trends in population-based survival rates for a wide range of childhood cancers in Britain during eras of entry to successive national and international trials during 1978-2005, the first 28 complete years of operation of the UKCCSG (known as the Children's Cancer and Leukaemia Group, CCLG, since 2006).

## Patients and Methods

Children with cancer diagnosed before the age of 15 years during 1978-2005 were ascertained from the population-based National Registry of Childhood Tumours (NRCT). Sources of notification were regional and national general cancer registries throughout Britain, specialist childhood cancer registries in several English regions, the register of patients under the care of CCLG members, entries to clinical trials, and death certification<sup>1</sup>. For this period there were 39,067 children resident in England, Scotland and Wales at diagnosis with any malignant neoplasm, or a non-malignant intracranial or intraspinal tumour.

The study included 25,853 children, 66% of all registered childhood cancers during 1978-2005 (Table 1). Diagnostic categories eligible for this study were defined as all those entities or combinations of entities in the third edition of the International Classification of Childhood Cancer (ICCC-3)<sup>17</sup> with an annual age standardised incidence above 1 per million children and for which there was a multi-centre trial of first-line treatment open to entry during a total of at least 10 years within the study period. We excluded children whose only source of information was a death certificate (n=122), since if they had survived they would not have been notified by any source. Numbers of eligible children are shown in Table 1 by diagnostic category. Since there were often separate trials for younger and older children with precursor-cell ALL, medulloblastoma and neuroblastoma, separate analyses were done for children in these categories according to the clinically relevant age thresholds of 1 year, 3 years and 1 year respectively.

The eras of successive trials for each diagnostic category were as shown in Table S1. For some diagnostic categories, the eras for analysis were defined according to the periods when trials were open for the largest clinical subgroup, namely ALL with low white blood count, B-cell NHL, stage IV neuroblastoma and non-stage IV rhabdomyosarcoma. In the mid 1980s, children with AML at several centres were included in the ‘Joint’ AML study outside the main series of MRC trials. Based on entry rates to the respective studies, we defined an era around this time from immediately after the date of closure of AML 8 (which had a higher entry rate than the ‘Joint’ study) until the date of closure of the ‘Joint’ study (which had a higher entry rate than AML 9). In addition to the trials listed in the table, about five children per year with Hodgkin lymphoma were included in the British National Lymphoma Investigation over a 14 year period from 1970<sup>5</sup> and limited numbers of centres participated in the first SIOP medulloblastoma trial<sup>18</sup> and the Intergroup Rhabdomyosarcoma Studies<sup>19;20</sup>.

For two trials of ALL and one each of Ewing sarcoma and germ cell tumours, the overall period of entry was split into sub-periods relating to major changes in protocol, as follows. In UKALL VIII, the single-arm ‘Study’ was superseded by a randomised trial in September 1981, in which patients would receive or not receive daunorubicin in the first two days of induction therapy; a further randomisation between two and three years of continuing therapy was introduced at the start of 1983<sup>21</sup>. Within ALL97, the duration and intensity of intensification treatment were changed and stratification by early bone-marrow response was introduced in November 1999, with the modified protocol being

known as ALL97/99<sup>22;23</sup>. For Ewing sarcoma, duration of continuing chemotherapy in ET-1 was halved from two years to one year as from 1982<sup>24</sup>. For germ cell tumours there was a major change in protocol during the first national study<sup>25</sup>, with the adoption of the 'BEP' chemotherapy regimen in 1983. In addition, the ENSG-5 protocol for stage IV neuroblastoma in children aged over 1 year was changed in November 1999 so that all patients still on treatment additionally received 6 months of treatment with cis retinoic acid<sup>26</sup>. Since the median duration of treatment excluding cis retinoic acid was about 29 weeks, this change would only have affected a minority even of patients diagnosed during the final few months that the trial was open. Consequently, we did not divide the period of this trial into sub-periods.

Follow-up was through linkage to death certificates of children dying from cancer and through flagging of survivors in the National Health Service Central Registers (NHSCR)<sup>1</sup>, and was virtually complete to 31 August 2010. With the exception of 119 children (0.5%) who were not known to have died and were untraced at NHSCR (n=40) or had emigrated (n=79), all survivors had at least 4 years of follow-up.

Actuarial survival was calculated by the Kaplan-Meier method, with log-rank tests for heterogeneity of survival between pairs of successive eras<sup>27</sup>; results of these tests are only presented where there were at least 5 deaths expected in each era. Time trends in survival were analysed by Cox regression<sup>28</sup>. Change in risk of death was defined as 1 minus the hazard ratio. Results for time trends are only presented for eras within which at least 10 deaths have occurred. All survival analyses were carried out using Stata version 9.2<sup>29</sup>.



## Results

Survival increased significantly with date of diagnosis during 1978-2005 for every diagnostic category studied. The annual reduction in risk of death ranged from 2.7% for rhabdomyosarcoma to 12.0% for gonadal germ cell tumours (Table 2).

The percentages of children in trials varied widely between diagnostic categories and between eras (Table S2). For most categories there was a tendency for entry rates to be higher in more recent eras. The highest entry rates, above 90%, were found for neuroblastoma (age <1 year) in 1992-99 and for Wilms tumour in 1991-2001 and 2002-2005. Consistently low entry rates, below 25%, were found for medulloblastoma before 1992 and after 2000.

There were steady reductions in risk of death between trial eras for many diagnostic categories (Table S2, Figs. S1-S17), notably ALL (age 1-14, Fig.1). For neuroblastoma (age 1-14), there was no consistent trend in survival before 1990 but a marked increase thereafter (Fig.2). For several other groups including and Ewing sarcoma of bone (Fig.3), survival increased until the mid 1980s but showed little further change since then.

There were significant increasing trends in survival within one or more eras for ALL age 1-14 years (two eras), AML, Hodgkin lymphoma, NHL (two eras), neuroblastoma age 1-14 years, Wilms tumour, hepatoblastoma, osteosarcoma, Ewing sarcoma of bone, gonadal germ cell tumours and other extracranial, extraspinal germ cell tumours (Table S2).

There were also significant trends during the 12 years before the start of the first trial for hepatoblastoma, the 11 years before the start of the first trial for rhabdomyosarcoma, and the three-year period between closure of trial 80931 and opening of EURAMOS for osteosarcoma (Table S2).

For ALL (age 1-14) within the era of UKALL VIII, five-year survival rates in the ‘Study’ (September 1980 to October 1981) and ‘Trial’ (November 1981 to December 1984) sub-periods were 67% and 70% respectively, and the difference between the survival curves was non-significant. Within the era of ALL97, five-year survival rates in the sub-periods of ‘ALL97’ (March 1997 to October 1999) and ‘ALL97/99’ (November 1999 to November 2002) were 85% and 88% respectively, and the difference between the survival curves was significant ( $p = 0.0487$ ). This improvement coincided with the adoption in the national trial of several changes in treatment, including use of dexamethasone and more intensive asparaginase scheduling, inclusion of early bone marrow response in risk stratification and a change in the backbone of treatment to include a more protracted period of consolidation chemotherapy, used in contemporaneous regimens internationally.

Survival of children with Ewing sarcoma was significantly higher in the second sub-period of the era of ET-1 compared with the first ( $p = 0.0116$ ), with five-year survival increasing from 33% to 45%; this difference was largely attributable to an increase from 47% to 61% in the probability that children who had survived the first year since

diagnosis would survive a further two years. Again, the time trend of survival within each sub-period was non-significant.

Survival differed significantly between the two sub-periods within the era of GC-1 both for gonadal germ cell tumours ( $p = 0.0075$ ) and for other extracranial, extraspinal germ cell tumours ( $p = 0.0079$ ); five-year survival rates during the two sub-periods were 78% and 90% respectively for gonadal tumours and 44% and 73% for non-gonadal tumours. For gonadal tumours there was a significant trend in survival with date of diagnosis during the first sub-period ( $p=0.0190$ ). The other time trends of survival within sub-periods were non-significant.

There was no major protocol change for Wilms tumour during the era of UKW3. Five-year survival during the first half of that era was 81%, lower than the 85% survival during the era of the previous trial, but it rose to 93% during the second half.

## Discussion

During the first 28 complete years of existence of the CCLG, the national professional grouping for paediatric oncology, two thirds of children with cancer were in diagnostic categories for which there was a national or international trial open to entry for a total of at least 10 years. Population-based survival increased significantly during this period for all of these categories, with the most impressive reductions in risk of death being achieved for germ cell tumours and hepatoblastoma. These improvements reflect advances in diagnostic techniques and revolutionary changes in treatment.

Recent patients are likely to have been diagnosed more accurately than patients at the beginning of the period. For example, the increase in survival from medulloblastoma may have been overstated since the data for earlier years probably include unrecognised cases of atypical teratoid/rhabdoid tumour (ATRT), which has a very poor prognosis<sup>30</sup> and occurs mainly among very young children<sup>31</sup>. When the analyses were repeated for all embryonal cerebellar tumours, virtually all of which are medulloblastoma or ATRT, the trends in survival by date of diagnosis remained significant for age groups 0-2 years ( $p=0.0111$ ) and 3-14 years ( $p<0.0001$ ).

Recent patients in some diagnostic groups may also have been diagnosed at an earlier stage of disease than patients from earlier years. In particular, recent cases of neuroblastoma among infants may include a higher proportion of cases that previously would have regressed spontaneously without ever being diagnosed. If so, the true improvement in survival for neuroblastoma among infants may be slightly overstated by the results presented here.

The extent of changes in population-based survival between successive trial eras largely parallels the improvement (or lack of improvement) reported by the relevant clinical trials. For ALL (age 1-14), population-based survival always increased between the eras of successive trials. Event-free survival was identical within the UKALL X and UKALL XI trials<sup>32</sup>, whereas overall eight-year survival increased from 74% in UKALL X to 81% in UKALL XI, largely as a result of more effective treatment for relapsed ALL in the UKALL R1 study which ran from 1991 to 1995<sup>33</sup>. It seems likely, therefore, that the

increase in population-based survival also reflects improved results of treatment for relapse.

For several diagnostic groups that were renowned for their poor prognosis until relatively recently, increases in population-based survival closely followed the improvements recorded by the trials themselves. For ALL in infants, successive large increases in survival corresponded to the introduction of the first national protocol specifically aimed at this biologically distinct form of the disease in 1992<sup>34</sup> and of the first multinational trial in 1999<sup>35</sup>. Survival from AML increased steadily from 1988 with AML10 and 1995 with AML12<sup>36</sup>. For neuroblastoma (age 1-14) there was a marked and sustained improvement in survival following introduction of intensive induction chemotherapy regimens and increasing use of high dose therapy consolidation as standard from the early 1990s<sup>26</sup>. Survival from hepatoblastoma almost doubled with the introduction of the first multinational clinical trial protocol for this very rare disease in 1990<sup>37</sup>.

There were several instances of a distinct absence of improvement in survival between the era of one trial and the next. Survival of ALL in infants decreased non-significantly between 1985-88 and 1989-91, corresponding to the lower event-free survival of infants treated on the Infant-87 pilot protocol compared with UKALL X<sup>38</sup>. Only one statistically significant decrease in survival from one era to the next was seen, for neuroblastoma (age 1-14) between 1982-85 (158 patients) and 1985-86 (85 patients). We ascribe this borderline significant result ( $p=0.0489$ ) to a chance finding among multiple comparisons. For children with osteosarcoma there was a non-significant decrease in survival between

1983-86 and 1986-93, followed by a moderate increase in 1993-2002, with the net result that five-year survival rose only from 55% to 57% between the first and last of the three eras. Five-year survival rates in the corresponding trials were also all around 55% to 58%<sup>39-41</sup>. For Ewing sarcoma of bone, population-based five-year survival was 67% in the era of ET-2 and 64% in the era of EICESS-92. Within ET-2, five-year survival for patients of all ages was 62%<sup>42</sup>. Five-year survival for all patients combined was not quoted in the report of EICESS-92<sup>43</sup> but a simple weighted average of the results for the standard risk and high risk groups indicates that it was also close to 62%.

Where a trial was substantially modified during its currency, there was sometimes, but not always, a significant difference in population-based survival between the sub-periods corresponding to the original and modified protocols. The absence of significant change in population-based survival for children with ALL between the eras of the UKALL VIII 'Study' and 'Trial' corresponded to the similarity of disease-free survival between the two sub-periods within that study<sup>21</sup>. Five-year survival within the ALL97 trial rose from 83.5% for the original protocol to 88% for ALL97/99, an improvement which was ascribed to multiple factors, including use of dexamethasone, optimised scheduling of asparaginase, a more protracted period of consolidation therapy for all patients and the adoption of risk stratification by early bone-marrow response<sup>23</sup>. The increase in population-based survival between the same two sub-periods was slightly less, from 85% to 88%.

For Ewing sarcoma, population-based survival increased after the change in the ET-1 protocol, whereas within the trial no difference in outcome was observed between the two sub-periods<sup>24</sup>. The trial included patients up to age 40 years, however, and results of the two versions of the protocol were not specifically reported for children. The increase in population-based survival was certainly not due to change in entry rates to the trial, since the proportions of children who were entered were very similar during the two sub-periods, 41% and 43% respectively.

The marked increase in survival for germ cell tumours in the second part of the era of GC-1 probably reflects the greater efficacy of the BEP regimen, which was also less toxic<sup>25</sup>.

In addition to the major changes to protocols discussed above, factors contributing to increases in survival within trial eras probably include wider participation in trials, increasing experience with treatment regimens, and developments in management of relapse. It is plausible that increasing survival from NHL during 1985-1989 was related to an increasing trend in the probability of entry to the NHL-2 trials; 59% of children with NHL or mature B-cell leukaemia were entered in a trial during 1985-1987, compared with 74% during 1988-1989. For neuroblastoma during the period of 1990-1999 when ENSG-5 was open to children with stage 4 disease, interpretation is complicated by the opening of several other trials for lower stage disease from 1993 onwards. Variation over time in the proportion of children with neuroblastoma for whom stage was known precluded analyses of trends in survival and trial entry for children with

different disease stages. Increasing use of MIBG scanning for staging may also have influenced the proportion labelled as metastatic disease. It seems likely that the improved results of treatment for relapsed ALL were responsible not only for the increase in survival between the eras of UKALL X and UKALL XI but also for the increasing trend within the era of UKALL X.

The increase in survival for Wilms tumour during the era of the UKW3 trial is exaggerated by the fall in survival in the early years of this trial compared with the era of the UKW2 trial. This may have been due to initial unfamiliarity with the pre-operative chemotherapy approach that was introduced in UKW3. An additional factor may be that at the beginning of the 1990s, management of relapsed Wilms tumour was not standardised and treatment was generally unsuccessful, perhaps because a non-intensive approach to first relapse was used<sup>44</sup>. National guidelines for the treatment of relapse with a standardised and intensive treatment approach were developed in 1998.

Diffusion of breakthrough developments in treatment for some adult cancers can take more than a decade<sup>45</sup>. In this study of a wide range of childhood cancers, the most dramatic increases in survival occurred much more immediately. This is not surprising, given the high proportions of children enrolled in trials and the fact that most non-trial patients would have been treated at the same limited number of paediatric oncology centres, using the standard arm of the current trial as best practice. We found no evidence that absence of a trial resulted in worsening of survival at the population level, although periods without an open trial between studies were generally short, resulting in



too few patients for formal comparisons. Since implementation of the EU Clinical Trials Directive in 2004 comprehensive trial portfolios are no longer available and intervals between trials have increased. As data for recent years mature it will be important to investigate the effects on survival from childhood cancer at the population level in relation to trial entry, to address the important question of whether patients who participate in clinical trials have better outcomes than those who do not.

### Funding

This work was supported by the Department of Health, the Scottish Government and CHILDREN with CANCER UK. The views expressed here are those of the authors and not necessarily those of the Department of Health, the Scottish Government or CHILDREN with CANCER UK.

### Disclosure

The authors have declared no conflicts of interest.

### Acknowledgements

We thank the regional and national cancer registries of England, Wales and Scotland, regional childhood tumour registries, the Children's Cancer and Leukaemia Group, the Clinical Trial Services Unit and the NHS Central Registers for providing data to the National Registry of Childhood Tumours.

**Table 1. Numbers of children in the analyses by diagnostic group (ICCC-3)<sup>17</sup>**

<b>ICCC-3 categories</b>			
Ia, division 1	Precursor-cell ALL		9747
		(Age <1 year	343)
		(Age 1-14 years	9404)
Ib	AML		1865
IIa	Hodgkin lymphoma		1689
Ia, division 2; IIb, IIc	NHL including Burkitt lymphoma and mature B-cell leukaemia (excluding mycosis fungoides)		2210
IIIc, division 1	Medulloblastoma		1473
		(Age 0-2 years	299)
		(Age 3-14 years	1174)
IVa	Neuroblastoma		2353
		(Age <1 year	721)
		(Age 1-14 years	1632)
VIa, division 1	Wilms tumour (excluding rhabdoid renal tumour, clear cell sarcoma of kidney, and other malignant renal tumours)		1968
VIIa	Hepatoblastoma		281
VIIIa	Osteosarcoma		886
VIIIc	Ewing tumour and related sarcomas of bone		709
IXa	Rhabdomyosarcoma		1483
Xa	Intracranial and intraspinal germ cell tumours (excluding benign teratoma and dermoid cyst)		341
Xc	Gonadal germ cell tumours		557
Xb	Other extracranial, extraspinal germ cell tumours		291
	Total		25853

**Table 2. Annual reduction in risk of death during 1978-2005 (ARR) and result of test for trend in survival by date of diagnosis**

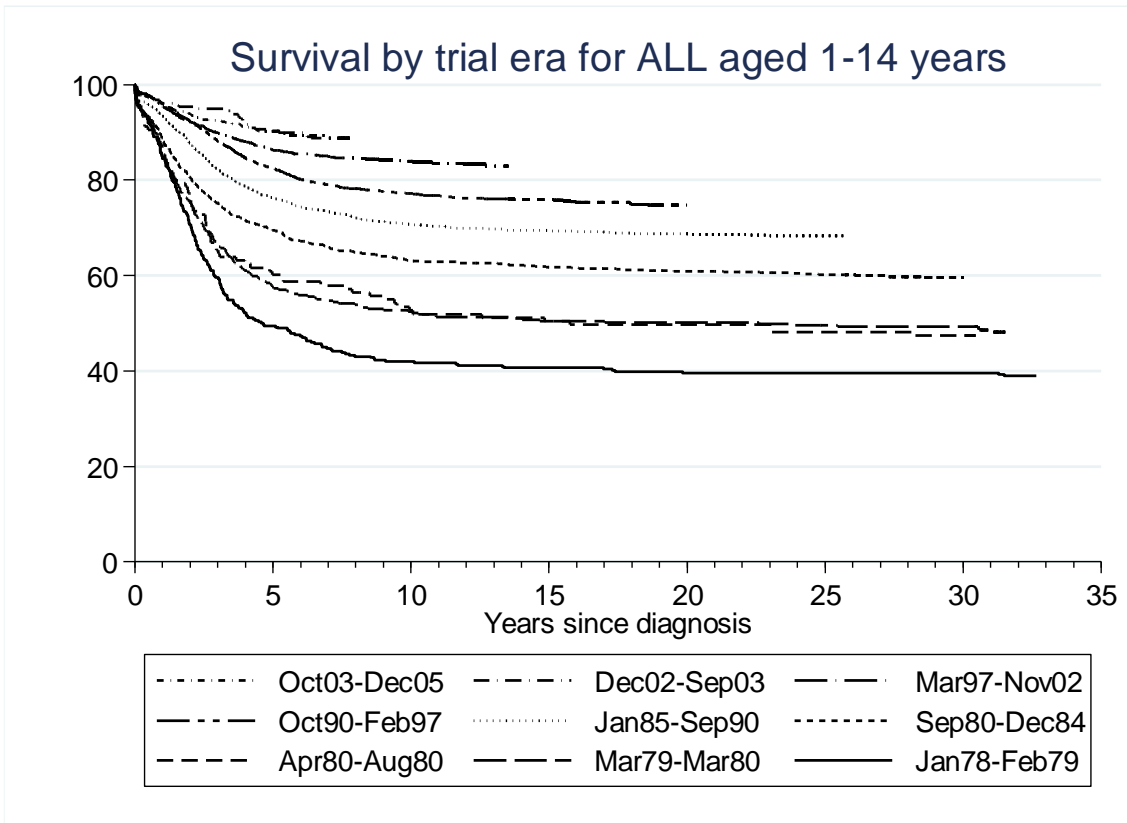
<b>Diagnostic group</b>	<b>ARR (%)</b>	<b>P (trend)</b>
ALL age <1 year	4.6	<0.0001
ALL age 1-14 years	6.1	<0.0001
AML	6.0	<0.0001
Hodgkin lymphoma	3.3	0.0003
NHL and mature B-cell leukaemia	5.2	<0.0001
Medulloblastoma age 0-2 years	3.0	0.0010
Medulloblastoma age 3-14 years	4.0	<0.0001
Neuroblastoma age <1 year	5.8	<0.0001
Neuroblastoma age 1-14 years	4.3	<0.0001
Wilms tumour	4.0	<0.0001
Hepatoblastoma	7.8	<0.0001
Osteosarcoma	3.0	<0.0001
Ewing sarcoma of bone	4.1	<0.0001
Rhabdomyosarcoma	2.7	<0.0001
CNS germ cell tumours	6.5	<0.0001
Gonadal germ cell tumours	12.0	<0.0001
Other extracranial, extraspinal germ cell tumours	7.9	<0.0001

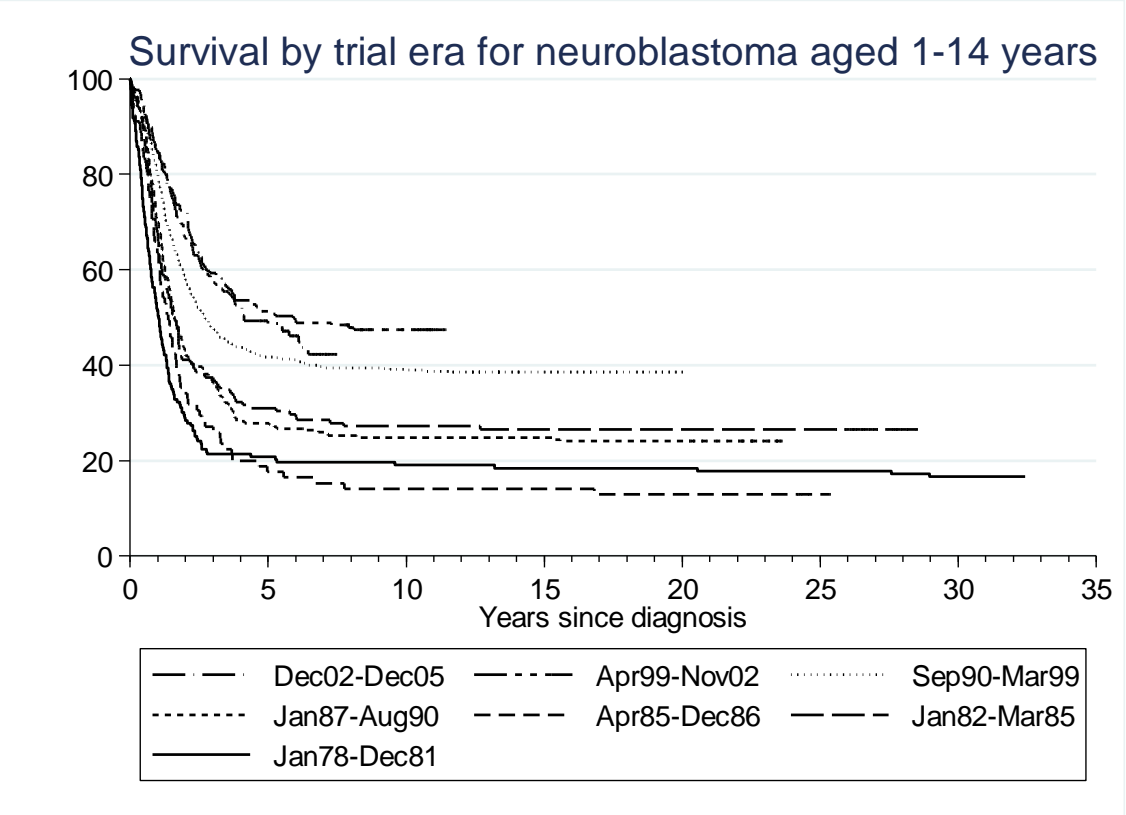
## **Titles of Figures**

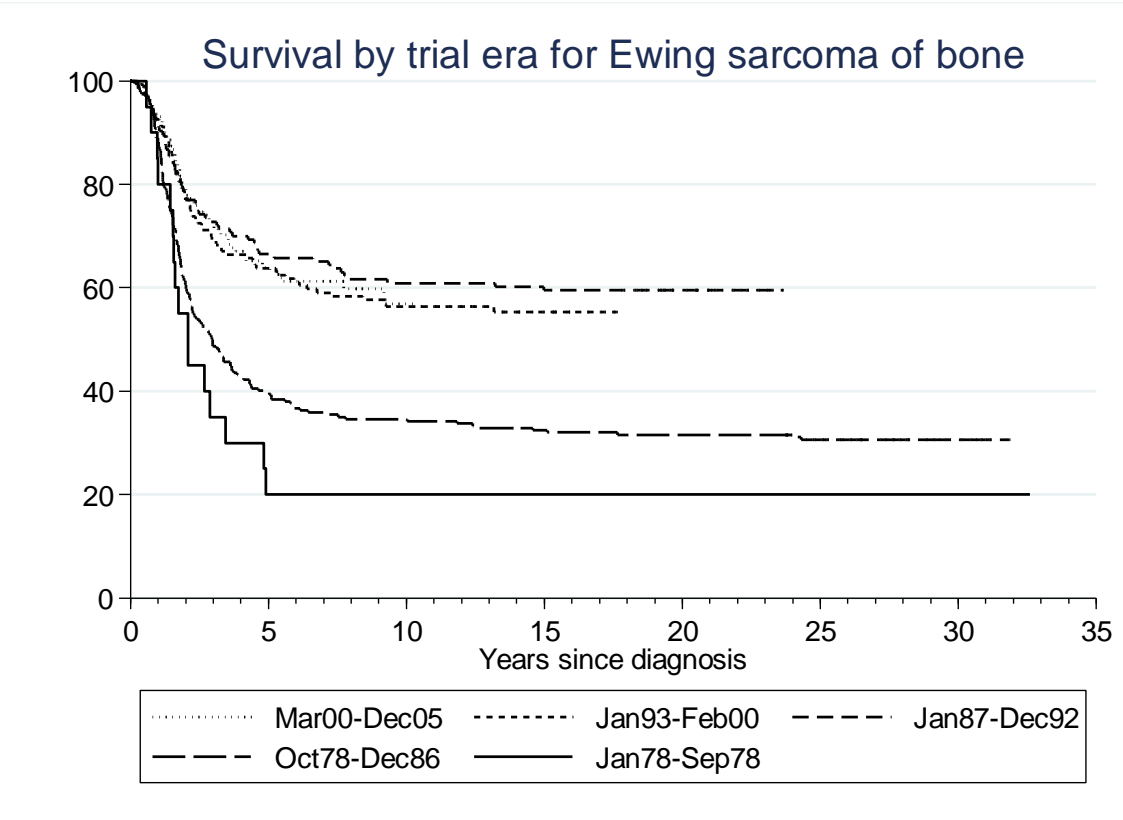
Figure 1. Population-based survival by trial era for children in Great Britain diagnosed at age 1-14 years with acute lymphoblastic leukaemia in 1978-2005. Numbers of patients by era were: 1/1978-2/1979, 375; 3/1979-3/1980, 360; 4/1980-8/1980, 136; 9/1980-12/1984, 1295; 1/1985-9/1990, 1818; 10/1990-2/1997, 2213; 3/1997-11/2002, 2105; 12/2002-9/2003, 278; 10/2003-12/2005, 824.

Figure 2. Population-based survival by trial era for children in Great Britain diagnosed at age 1-14 years with neuroblastoma in 1978-2005. Numbers of patients by era were: 1/1978-12/1981, 183; 1/1982-3/1985, 158; 4/1985-12/1986, 85; 1/1987-8/1990, 262; 9/1990-3/1999, 547; 4/1999-11/2002, 215; 12/2002-12/2005, 182.

Figure 3. Population-based survival by trial era for children in Great Britain diagnosed at age 0-14 years with Ewing sarcoma of bone in 1978-2005. Numbers of patients by era were: 1/1978-9/1978, 21; 10/1978-12/1986, 237; 1/1987-12/1992, 144; 1/1993-2/2000, 149; 3/2000-12/2005, 158.







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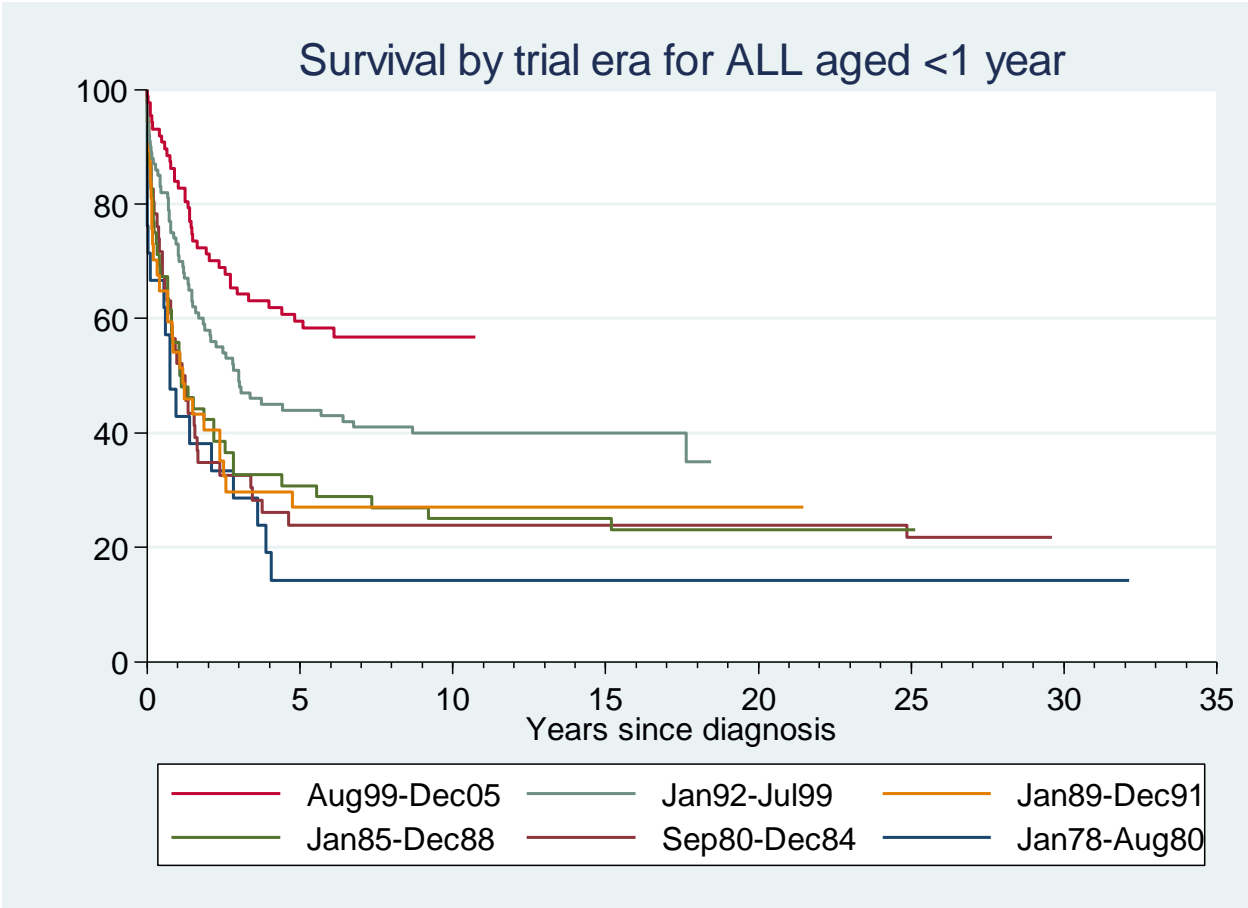
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Figure S1. Population-based survival by trial era for children in Great Britain diagnosed at age under 1 year with acute lymphoblastic leukaemia in 1978-2005.



**Table S1.****National and international trials for newly diagnosed childhood cancer open in Great Britain during 1978-2005**

<b>Diagnostic group</b>	<b>Period of entry</b>	<b>Trial</b>	<b>Reference</b>	
ALL age <1 year	9/1980-12/1984	UKALL VIII	21;38	
	1/1985-12/1988	UKALL X	38;46	
	1/1992-7/1999	Infant 92	34	
	8/1999-12/2005	Interfant-99	35	
	ALL age 1-14 years	1/1976-2/1979	UKALL V	47
1/1978-3/1980		UKALL VI	48	
3/1979-3/1980		UKALL VII	49	
9/1980-12/1984		UKALL VIII	21	
1/1985-9/1990		UKALL X	46	
10/1990-2/1997		UKALL XI	50	
3/1997-11/2002		ALL 97	22;51	
10/2003-12/2005		ALL 2003		
AML		12/1974-4/1980	UKAML	52
		5/1980-5/1983	AML 8	53
	1/1983-3/1987	Joint AML	54	
	1/1984-4/1988	AML 9	55	
	5/1988-3/1995	AML 10	56	
	4/1995-5/2002	AML 12	57	
	6/2004-12/2005	AML 15		
	Hodgkin Lymphoma	1/1982-5/1992	UKCCSG HD-1	58
6/1992-12/1999		UKCCSG HD-2	59	
1/2000-3/2005		UKCCSG HD-3	60	
NHL	7/1977-7/1983	NHL-1	8;9	
	8/1985-12/1989	NHL-2	61-64	
	1/1990-3/1996	NHL-3	64-66	
	4/1996-6/2001	FAB/LMB 96	67-69	
	5/1995-2/2000	T-cell		
	8/1998-3/2000	ALCL 98		
	4/2000-12/2005	ALCL 99	70;71	
	9/2004-12/2005	Euro-LB-02 (T-NHL)		
	Medulloblastoma age 0-2 years	9/1978-5/1983	BT-1	
		1/1984-12/1989	PNET-2	72
6/1992-9/1996		Infant brain tumour	73	
6/2001-11/2003		Infant PNET		
Medulloblastoma age 3-14 years	9/1978-5/1983	BT-1		
	1/1984-12/1989	PNET-2	72	
	4/1992-8/2000	PNET-3	74;75	
	12/2003-12/2005	PNET-4		

Neuroblastoma age <1 year	1/1982-3/1985	ENSG-1	76
	9/1992-6/1999	ENSG-8	
	7/1999-6/2004	European Infant Neuroblastoma	77-79
Neuroblastoma age 1-14 years	1/1982-3/1985	ENSG-1	76
	4/1985-12/1986	ENSG-3*	80;81
	9/1990-3/1999	ENSG-5	26
	1/1993-3/1995	ENSG-6	
	7/1993-7/1995	ENSG-7	
	3/1995-11/2000	ENSG-9	
	7/1995-6/1999	LNESG-1†	82;83
	4/1999-10/2003	Kushner	84
	12/2000-12/2005	SIOPEN unresectable localised	
Wilms tumour	12/2002-12/2005	SIOPEN-HR-NBL1	85
	7/1974-10/1978	MRC 2	86
	1/1980-12/1985	UKW 1	87
	1/1986-9/1991	UKW 2	88
	10/1991-3/2001	UKW 3	89
Hepatoblastoma	3/2002-12/2005	SIOP 2001	
	1/1990-2/1994	SIOPEL 1	37
	10/1995-5/1998	SIOPEL 2	90
	6/1998-12/2005	SIOPEL 3	91;92
Osteosarcoma	7/2004-12/2005	SIOPEL 4	
	2/1975-7/1981	MRC	93
	7/1983-6/1986	80831	39
	7/1986-4/1993	80861	40
	5/1993-9/2002	80931	41
Ewing sarcoma of bone	9/2005-12/2005	EURAMOS	
	10/1978-12/1986	ET-1	24
	1/1987-12/1992	ET-2	42
	1/1993-2/2000	ECESS-92	43
Rhabdomyosarcoma	3/2000-12/2005	Euro Ewing 99	94;95
	1/1989-6/1995	MMT89	96;97
	7/1995-6/2003	MMT95	98
	11/1998-11/2004	MMT98	99
Intracranial & intraspinal germ cell	1/1989-12/1996	GC-2	
	1/1997-12/2005	SIOP	
Extracranial, extraspinal germ cell	1/1979-12/1988	GC-1	25
	1/1989-4/2004	GC-2	100
	5/2005-12/2005	GC-3	

\* ENSG-3C was open until November 1987, but no British patients were entered after the end of 1986

† LNESG-1 was also open to infants, but only one British patient aged under a year at diagnosis was entered



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**Table S2. Numbers of cases analysed, percentage included in trials and five-year survival (%) by era, with results of tests for difference in survival from previous era and trend in survival within era**

<b>Diagnostic group</b>	<b>Period of diagnosis</b>	<b>Number of cases</b>	<b>% in trials</b>	<b>5 year survival</b>	<b>P (difference)</b>	<b>P (trend)</b>
ALL age <1 year	1/1978-8/1980	21	*	14		NS
	9/1980-12/1984	46	39	24	NS	NS
	1/1985-12/1988	52	48	31	NS	NS
	1/1989-12/1991	37	*	27	NS	NS
	1/1992-7/1999	100	80	44	NS	NS
	8/1999-12/2005	87	72	60	0.0217	NS
ALL age 1-14 years	1/1978-2/1979	375	68	49		NS
	3/1979-3/1980	360	51	58	0.0153	NS
	4/1980-8/1980	136	*	60	NS	NS
	9/1980-12/1984	1295	59	70	0.0070	NS
	1/1985-9/1990	1818	80	76	<0.0001	0.0400
	10/1990-2/1997	2213	87	82	<0.0001	NS
	3/1997-11/2002	2105	88	86	<0.0001	0.0403
	12/2002-9/2003	278	*	90	NS	NS
AML	10/2003-12/2005	824	85	90	NS	NS
	1/1978-4/1980	168	38	17		NS
	5/1980-5/1983	171	48	24	NS	NS
	6/1983-3/1987	231	47	30	NS	0.0015
	4/1987-4/1988	66	*	42	NS	NS
	5/1988-3/1995	458	67	51	NS	NS
	4/1995-5/2002	495	78	63	0.0001	NS
	6/2002-5/2004	162	*	66	NS	NS
Hodgkin lymphoma	6/2004-12/2005	114	30	67	NS	NS
	1/1978-12/1981	246	*	91		NS
	1/1982-5/1992	560	58	92	NS	0.0101
	6/1992-12/1999	441	68	95	0.0120	NS
	1/2000-3/2005	380	76	94	NS	NS
NHL and mature B-cell leukaemia	4/2005-12/2005	62	*	93		
	1/1978-7/1983	389	47	52		0.0494
	8/1983-7/1985	145	*	69	0.0058	NS
	8/1985-12/1989	329	66	72	NS	0.0039
	1/1990-3/1996	523	77	76	NS	NS
	4/1996-6/2001	453	75	79	NS	NS
Medulloblastoma age 0-2	7/2001-12/2005 <sup>†</sup>	371	14	84	NS	NS
	1/1978-8/1978	7	*	0		
	9/1978-5/1983	53	13	21	NS	NS
	6/1983-12/1983	5	*	80		
	1/1984-12/1989	59	17	42		NS
1/1990-5/1992	22	*	32	NS	NS	

	6/1992-9/1996	50	46	34	NS	NS
	10/1996-5/2001	54	*	43	NS	NS
	6/2001-11/2003	32	16	41	NS	NS
	12/2003-12/2005	17	*	44	NS	
Medulloblastoma age 3-14	1/1978-8/1978	37	*	43		NS
	9/1978-5/1983	223	23	42	NS	NS
	6/1983-12/1983	34	*	59	NS	NS
	1/1984-12/1989	225	19	45	NS	NS
	1/1990-3/1992	97	*	49	NS	NS
	4/1992-8/2000	332	69	68	0.0020‡	NS
	9/2000-11/2003	129	*	74	NS	NS
	12/2003-12/2005	97	9	67	NS	NS
Neuroblastoma age <1 year	1/1978-12/1981	80	*	65		NS
	1/1982-3/1985	71	11	79	NS	NS
	4/1985-8/1992	179	*	78	NS	NS
	9/1992-6/1999	183	93	82	NS	NS
	7/1999-6/2004	165	69	91	0.0159	NS
	7/2004-12/2005	43	*	91		
Neuroblastoma age 1-14 years	1/1978-12/1981	183	*	21		NS
	1/1982-3/1985	158	42	31	0.0032	NS
	4/1985-12/1986	85	39	18	0.0489	NS
	1/1987-8/1990	262	*	28	0.0295	NS
	9/1990-3/1999	547	73	42	<0.0001	0.0295
	4/1999-11/2002	215	28	51	0.0172	NS
	12/2002-12/2005	182	74	49	NS	NS
Wilms tumour	1/1978-10/1978	73	30	77		NS
	11/1978-12/1979	62	*	74	NS	NS
	1/1980-12/1985	377	81	81	NS	NS
	1/1986-9/1991	404	88	85	0.0070	NS
	10/1991-3/2001	676	94	87	NS	0.0001
	4/2001-2/2002	77	*	88	NS	
	3/2002-12/2005	299	92	90	NS	NS
Hepatoblastoma	1/1978-12/1989	86	*	35		0.0196
	1/1990-2/1994	47	89	64	0.0024	NS
	3/1994-9/1995	16	*	75	NS	NS
	10/1995-5/1998	31	74	77		NS
	6/1998-12/2005	101	82	76	NS	NS
Osteosarcoma	1/1978-7/1981	134	?	29		NS
	8/1981-6/1983	72	*	38	NS	NS
	7/1983-6/1986	75	56	55	0.0078	NS
	7/1986-4/1993	194	54	51	NS	NS
	5/1993-9/2002	316	42	57	NS	NS
	10/2002-8/2005	87	*	57	NS	0.0388
	9/2005-12/2005	8	38	-		
Ewing sarcoma of bone	1/1978-9/1978	21	*	20		NS
	10/1978-12/1986	237	42	40	NS	0.0031

	1/1987-12/1992	144	73	67	<0.0001	NS
	1/1993-2/2000	149	73	64	NS	NS
	3/2000-12/2005	158	82	64	NS	NS
Rhabdomyosarcoma	1/1978-12/1988	573	*	54		0.0296
	1/1989-6/1995	366	75	63	0.0007	NS
	7/1995-6/2003	413	85	67	NS	NS
	7/2003-12/2005 <sup>§</sup>	131	10	63	NS	NS
Intracranial & intraspinal germ cell	1/1978-12/1988	110	*	53		NS
	1/1989-12/1996	107	31	69	0.0280	NS
	1/1997-12/2005	124	72	86	0.0003	NS
Gonadal germ cell	1/1978-12/1978	24	*	71		
	1/1979-12/1988	207	51	86		0.0006
	1/1989-4/2004	294	74	96	<0.0001	NS
	5/2004-4/2005	19	*	100		
	5/2005-12/2005	13	31	100		
Other extracranial, extraspinal germ cell	1/1978-12/1978	6	*	17		
	1/1979-12/1988	74	65	62		0.0015
	1/1989-4/2004	181	75	83	0.0013	NS
	5/2004-4/2005	16	*	88		
	5/2005-12/2005	14	36	-		

\* Non- trial period

† In this period, trials were open for anaplastic large cell lymphoma and latterly for T-lymphoblastic NHL but not for B-cell NHL

‡ The difference in survival for all embryonal cerebellar tumours (medulloblastoma and ATRT) diagnosed at age 3-14 years between the periods 1990-1992 and 1992-2000 was also significant (p=0.0087)

§ A trial was open until November 2004 for stage IV rhabdomyosarcoma only

Figure S2. Population-based survival by trial era for children in Great Britain diagnosed at age 1-14 years with acute lymphoblastic leukaemia in 1978-2005.

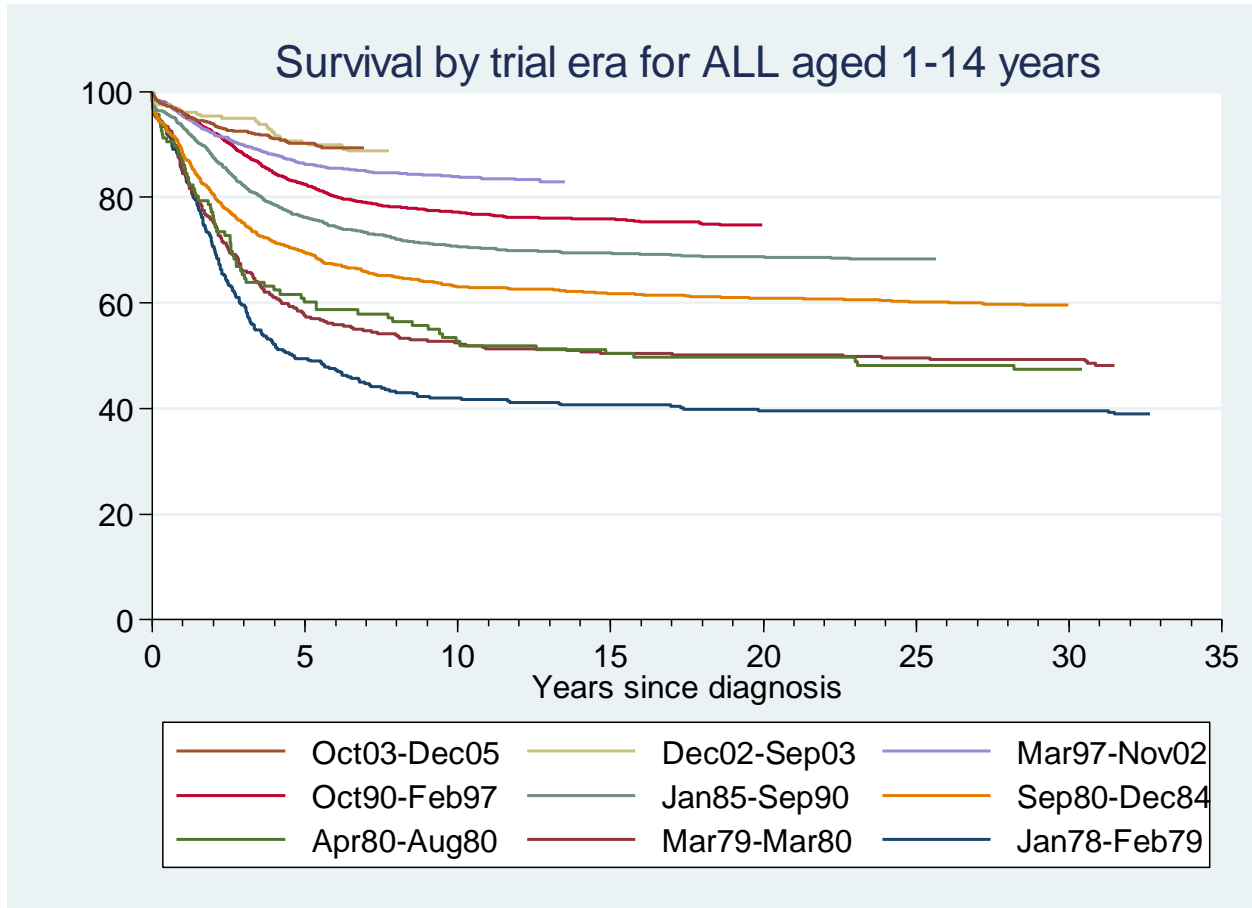


Figure S3. Population-based survival by trial era for children in Great Britain diagnosed at age 0-14 years with acute myeloid leukaemia in 1978-2005.

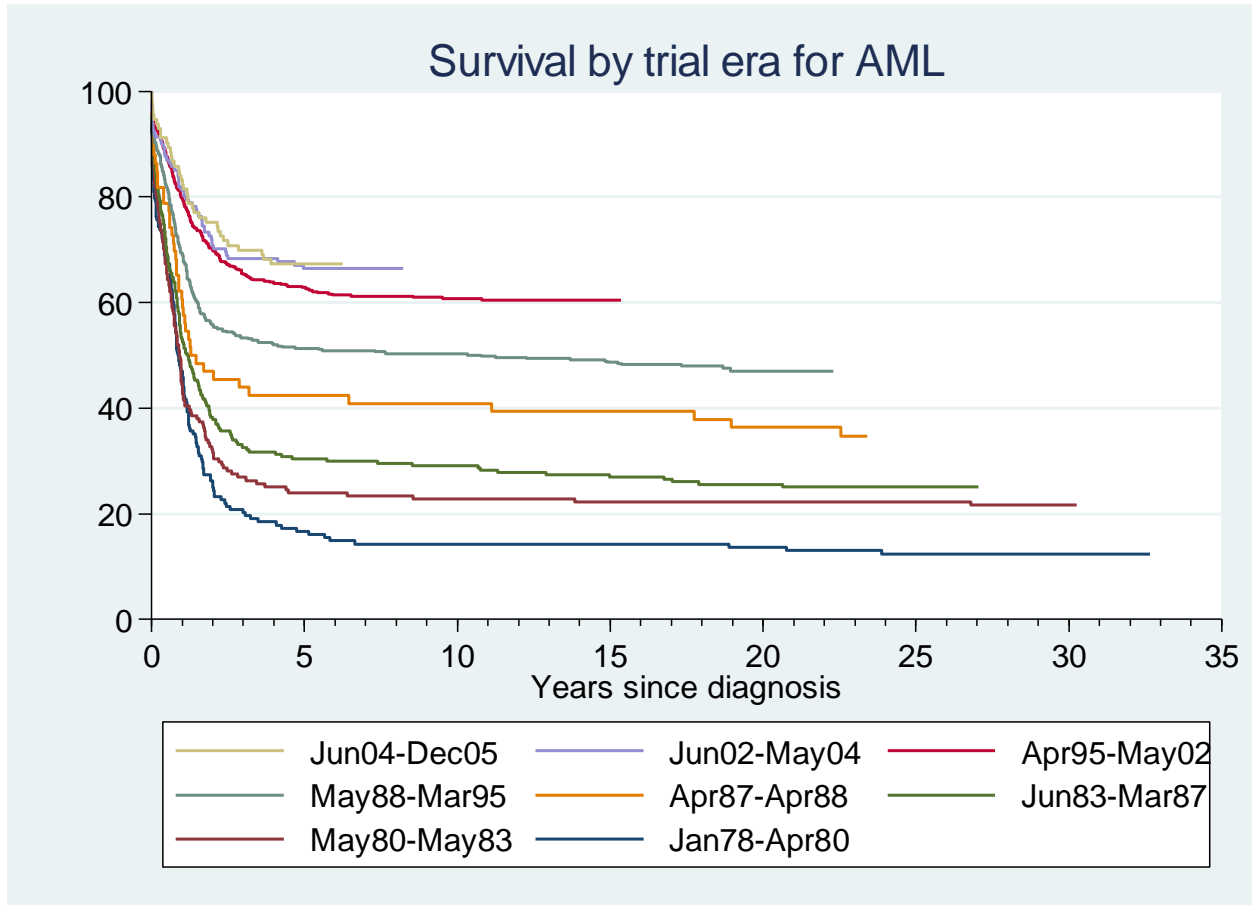


Figure S4. Population-based survival by trial era for children in Great Britain diagnosed at age 0-14 years with Hodgkin lymphoma in 1978-2005.

