A population based cytogenetic study of adults with acute lymphoblastic leukaemia (ALL).

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Abstract

Chromosomal abnormalities are increasingly used to risk stratify adults with ALL. Published data describing the age-specific incidence of chromosomal abnormalities and their prognostic relevance is largely derived from clinical trials. Trials frequently have age restrictions and low recruitment rates. Thus we investigated these factors in a population-based cohort of 349 patients diagnosed over 19 years in the North of the UK. The incidence of most chromosomal abnormalities varied significantly with age. The incidence of t(9;22)(q34;q11) increased in each successive decade, up to 24% among 40-49 year olds. Thereafter the incidence reached a plateau. t(4;11)(q21;q23) and t(1;19)(q23;p13) were rare among patients aged over 60 years. In contrast, t(8;14)(q24;q32) and t(14;18)(q32;q21) increased with age. High hyperdiploidy occurred in 13% of patients <20 years but in only 5% of older patients. The incidence of low hypodiploidy / near–triploidy (HoTr) and complex karyotype increased with age from 4% (15-29 years) to 16% (60+ years). Overall survival varied significantly by age and cytogenetics. Older patients and those with t(9;22), t(4;11), Ho-Tr or complex karyotype had a significantly inferior outcome. These population-based results demonstrate the cytogenetic heterogeneity of adult ALL. These data will inform service planning and the design of new age-focussed clinical trials.

Introduction

Recurrent and clonal chromosomal abnormalities in the leukaemic cells of patients with acute lymphoblastic leukaemia (ALL) are the hallmark of the disease and are now routinely used in the paediatric setting to assist patient management, particularly in terms of diagnosis, disease monitoring, prognosis and risk stratification.[1] The clinical utility of cytogenetics in adult ALL is an emerging topic and more studies are urgently required.[2,3] To date the majority of cytogenetic studies (paediatric and adult) have been based on patients enrolled to local, national or international clinical trials. In paediatric ALL these studies can be considered representative because recruitment rates in this age group are very high. However, trial recruitment is much lower among adolescents and adults.[4] Moreover, adults aged over 60 years are rarely eligible for clinical trials.[5,6] Population-based studies of adult ALL are rare. The lack of studies describing the age-specific incidence of chromosomal abnormalities and their prognostic relevance makes planning services and clinical trials difficult. There are several current issues which would benefit significantly from such data: (1) The treatment of adolescents and young adults is controversial with many clinical trial groups opting to treat them on paediatric protocols.[7-10] However, the distinct genetic profile of these patients has not been taken into consideration.[11] (2) There is renewed interest in developing treatment protocols for older (more than 60 years old) adults[12]; (3) Recent studies have demonstrated that

cytogenetics is highly predictive of outcome in adult ALL but the effectiveness of these markers has not been tested outside clinical trials.[2,3] In this report we present population-based cytogenetic, clinical and outcome data from 349 adult ALL patients diagnosed over a 19 year period in a single region of the North of England.

Patients and Methods

Study Area and Population data

The study area comprised the region served by the NHS North East Strategic Health Authority during this period. The total population of this region is 3.1 million and includes 2.5 million people aged 15 years old or more (Office for National Statistics - http://www.statistics.gov.uk/). Age-specific incidence rates were calculated using the average of the population determined by the 1991 and 2001 UK censuses (Office for National Statistics). Since October 1982, the consultant haematologists in this region have collaborated to keep a register of all newly diagnosed patients with ALL.[5] Ethical approval to conduct this audit was granted by the relevant treatment centres.

Diagnosis

All patients diagnosed between 1st January 1983 and 31st December 2001 with ALL and aged 15 years or more were included in this study. In all cases, the diagnosis was confirmed by morphology and appropriate cytochemical staining. Immunophenotyping was performed where possible using standard methodologies and cases were retrospectively classified into one of five subgroups (pro-B, BCP-ALL, mature-B, T-ALL and biphenotypic) using the original immunological classification.

Cytogenetics

Cytogenetic studies were performed at one of three laboratories in the region (see acknowledgements) but collated by the NHS Northern Genetics Service. Analysis was performed on pre-treatment bone marrow or peripheral blood samples using standard G-banding techniques. Screening for the major chromosomal translocations [t(9;22)/*BCR-ABL1*, *MLL*/11q23 rearrangements] using fluorescence in situ hybridisation (FISH) and/or Reverse-transcriptase Polymerase Chain Reaction (RT-PCR) assays became routine practice at the beginning of 1997. Chromosomal abnormalities were defined and recorded according to the International System for Human Cytogenetic Nomenclature (ISCN).[13] None of the patients presented in this report were included in the previous cytogenetic study of patients treated on MRC UKALLXII/ECOG2993.[2]

Treatment

Patients under the age of 55 years with ALL (B-cell precursor, T-cell and mature-B) or acute biphenotypic leukaemia, who were treated with curative intent, were mostly treated according to regional North East ALL protocols (NE-ALL III-VI).[14,15] Occasionally patients were treated according to, but not registered on, national protocols (UKALLXII, UKALLXA)[16,17]. Acute biphenotypic leukaemia was defined as terminal deoxynucleotidyl transferase (TdT) positive patients who also expressed some myeloid antigens. In this era TdT positivity was considered the key marker indicating involvement of the lymphoid lineage and hence ALL therapy. The multi-agent protocol NE-ALL III[15] was introduced in 1982 and correlates with the start of this study. In 1984, routine standard maintenance was stopped for patients under 55 years and instead these patients were offered, in first remission, an allogeneic transplant or, in the absence of a family donor, an autologous transplant.[14] Patients under 45 years underwent a preconditioning regimen of cyclophosphamide (60mg/Kg) and total body irradiation (1200cGy) and those aged 45-55 years received melphalan (3mg/Kg), total body irradiation (1050cGy) and non-cryopreserved marrow rescue. Between 1988-1994 (NE-ALL IV–V), idarubicin replaced adriamycin in induction because of improved penetration into the CNS, and prednisolone was replaced by dexamethasone. Cranial irradiation was used throughout NE-ALL III-V unless the patient received irradiation as part of their conditioning for a transplant. The last NE-ALL protocol in the series (NE-ALL VI) started in 1994. Cranial irradiation was abandoned and replaced by a consolidation phase in which two courses of high dose methotrexate were alternated with two courses of high dose iphosphamide, epirubicin and etoposide (IVE). The transplant policy in NE-ALL VI was the same as NE-ALL IV-V and applied consistently until 2001. Patients aged 55 years or more were treated as previously described.[5]

Statistics

Categorical variables were compared using the chi-square or Fisher exact tests. The Mann Whitney rank test was used to compare the age distribution of different cytogenetic subgroups. Complete remission (CR) was defined morphologically as fewer than 5% blasts in the bone marrow, immunologically as TdT/CD10 negativity (pre-1995) or by molecular assessment of immunoglobulin and T cell gene rearrangements (post 1995). Survival analysis was restricted to those patients who were treated using an intention to cure protocol (n=250). Patients who received only palliative care, those who presented with advanced organ failure and those who died before a CR could be assessed were deemed not to have received treatment with curative intent (n=99) and, therefore, were not included in the survival analysis. Overall survival (OS) was defined as the time from diagnosis to death or last contact. Survival estimates, life tables and curves were constructed by means of the Kaplan-Meier method. The variables age and

cytogenetic risk group were initially analysed in isolation using univariate Cox regression models. Multivariate Cox regression on these variables was then performed via a stepwise modelling process based on the difference between successive models calculated using the log likelihood. At this stage of analysis there was a further reduction of the number of patients analysed due to missing cytogenetics (n=73), dates (n=13) or because of statistical concerns over their excessive influence on the model (n=2). Thus a total of 162 patients were included in the multivariate model. Due to the exploratory nature of this analysis all calculations were considered at the 5% significance level.

Results

Descriptive epidemiology

A total of 349 adults aged 15 years or more were diagnosed with ALL during the study period. Although the number of patients diagnosed each year varied there was no trend towards either an increase or decrease in the incidence of the disease during the study period (Figure 1). The incidence of ALL varied by age and a bimodal distribution was observed with the younger (15-19) and older adults (70+ years) having the greatest incidence (Figure 2). Approximately one third of the patients were aged 60 years or more (Table 1).

Overall there were more males than females (1.2M:1F) but this ratio varied significantly with age ($p<0.03$) (Table 1, Figure 2). The excess of males was confined to younger adults where the ratio was 1.8M:1F. In addition, the excess of males was more pronounced in among T-ALL patients where a ratio of 2.2M:1F was observed. T-ALL patients were also younger (see below). Figure 2 shows the age-specific incidence of ALL for males and females separately, demonstrating that the change in the sex ratio with increasing age is not simply a function of the increased life expectancy enjoyed by females.

The majority of patients had a B-lineage ALL (240, 81%), while 42 (14%) had T-ALL and 15 (5%) were described as biphenotypic (see Methods). However, this distribution differed significantly with age ($p<0.001$) (Table 1). Patients with mature-B ALL, which comprised 11% of patients overall, were significantly older - median age 63 years (interquartile range (IQR) – 53 to 71 years) versus 42 years (IQR 23 to 66 years) ($p=0.0001$). In contrast, T-ALL patients were significantly younger - median age 25 years (IQR 19 to 42 years) versus 48 years (IQR 26 to 69 years) ($p=0.0001$).

White cell count (WCC) was strongly correlated with immunophenotype. Patients with T-ALL were significantly more likely to have a WCC of $>50x10^9$/L compared to B-lineage patients: 17/42 (40%) versus 47/247 (19%), p=0.001. Given that T-ALL were also significantly younger (see above), this translated into older patients appearing to have a lower WCC (Table 1). However, no such effect was seen if the T-ALL patients were excluded (data not shown).

Diagnostic cytogenetic analysis

Cytogenetic analysis was attempted in 292/349 (84%) patients but was significantly more prevalent after 1993: 160/171 (94%) versus 132/178 (74%) (p<0.001) (Table 1 & Figure 1). This was true across all age groups (data not shown). A total of 236 (81%) had a successful cytogenetic result and a clonal chromosomal abnormality was detected in 173 (73%) patients. These rates did not vary during the study period (p>0.05) or by age (p>0.05). Overall cytogenetics revealed a normal karyotype in 63 (27%) patients but this was more prevalent among T-ALL patients (14/30, 47%) compared to B lineage patients (38/176, 22%) (p=0.006). As T-ALL patients are younger this explains the higher incidence of normal karyotype in adolescents (15-19 years).

The most prevalent specific chromosomal abnormality was the Philadelphia chromosome [t(9;22)(q34;q11), *BCR-ABL1*] which was present in 36 (15%) patients. There was no difference in the incidence before and after the introduction of routine FISH/RT-PCR at beginning of 1997: 24/158 (15%) versus 12/92 (13%) (p>0.1). The prevalence increased with age up to, but not beyond, the fourth decade: 15-19 years 2/42 (5%), 20-29 years 4/35 (11%), 30-39 years 4/26 (15%), 40-49 years 7/29 (24%), 50-59 years 5/24 (21%), 60-69 years 8/38 (21%), 70-79 years 4/30 (13%), 80+ years 2/12 (17%). Thus while there was a significant difference in the incidence of t(9;22) between patients aged 15-30 years (7%) and those aged over 30 years (24%) (p=0.02), there was no difference between those aged 30-60 years (22%) and over 60 years (16%) (p=0.4). The majority of t(9;22) patients had BCP-ALL (32/35, 91%) but 3 patients were described as having a biphenotypic immunophenotype. Just over half the t(9;22) patients (19/34, 56%) had a WCC less than $50x10^9$/L while the remaining 15 patients had a WCC of more than $50x10^9$/L including 10 patients with a WCC of more than $100x10^9$/L.

Other established chromosomal translocations: t(4;11), t(1;19), t(8;14), t(14;18); each occurred in less than 10% of patients but showed strong correlations with age. Both t(4;11) and t(1;19) occurred more often in younger adults and t(8;14) and t(14;18) in

older adults (60+ years) (Table 2). The two ploidy subgroups, high hyperdiploidy (51-65 chromosomes, HeH) and low hypodiploidy/near triploidy (30-39 & 60-78 chromosomes, HoTr), were observed in 7% and 3% of patients, respectively. None of these patients had T-ALL or Mature-B ALL and they were associated with younger and older age, respectively (Table 2). Patients without one of the aforementioned established chromosomal abnormalities or tetraploidy were classified as having a complex karyotype, if five or more clonal chromosomal abnormalities were observed. This subgroup accounted for 7% of patients overall but was more prevalent among patients over 60 years old. Collectively, Philadelphia negative patients with high risk cytogenetics; defined as t(4;11), t(8;14), HoTr and complex karyotype[2], were significantly more prevalent among patients over the age of 60 years: 24/66 (36%) versus 25/134 (19%) (p=0.006).

The most prevalent cytogenetic subgroups were the other abnormal group and those with a normal karyotype which together accounted for more than 50% of patients with successful cytogenetics. Among the 59 patients classified as "other abnormal" some known chromosomal abnormalities were observed but were too infrequent to be analysed separately. Examples include, t(10;14)(q24;q11) (n=2) and t(11;14)(p13;q11) (n=1). Known secondary chromosomal abnormalities, such as deletions of 6q (n=9) and 9p (n=6), were also observed both in combination with established abnormalities and within the "other abnormal" and complex karyotype groups but at too low a frequency to be analysed separately.

Outcome and prognostic relevance of chromosomal abnormalities

Among the 349 patients in this cohort, 250 (72%) were treated with curative intent. This included 211/225 (94%) patients under the age of 60 years but only 39/124 (31%) of those over 60 years old. Only the outcome of patients who were actively treated have been considered in this section. A complete remission (CR) was achieved by 194/247 (78%) patients who were actively treated. However, this rate varied by age and cytogenetics (Table 1 and 2). Significantly fewer patients over the age of 60 years achieved a CR compared to those under 60 years: 20/39 (51%) versus 174/208 (84%) (p<0.001). In addition, fewer patients with t(9;22) or other high risk cytogenetics achieved a CR (Tables 1 and 2).

Among the 250 actively treated patients, 100 (40%) received a bone marrow transplant: autologous (n=66), allogeneic (n=29) or matched unrelated (MUD) (n=6). All but six of the transplants were performed in first CR. None of the patients over the age of 60 years

received a transplant compared with 59/115 (51%) 15-29 year olds and 41/110 (37%) 30-60 year olds. The remaining 99 patients received chemotherapy alone.

Given the duration of the study and the heterogeneity of treatments received, we have only considered overall survival. Recent data suggest that in adult ALL outcome after relapse is extremely poor[18]; hence this is a suitable endpoint to be considered by this study. The median follow-up time for this cohort was 6.25 years. The 5 year overall survival (OS) rate for the whole cohort was 30% (95% C.I. 24-36%). However, this figure varied considerably by age and cytogenetics (Tables 1 and 2, Figures 3 and 4). Estimates of the 5 year OS rates by each decade were as follows: 15-19 years 47% (95% CI 33-61%); 20-29 years 43% (95% CI 29-57%); 30-39 years 16% (6-32%); 40-49 years 20% (8-36%); 50-59 years 19% (7-36%); 60+ years 12% (3-27%). Older patients and those with poor risk cytogenetics, as defined by the MRC UKALLXII / ECOG 2993 trial, had a significantly worse outcome (Tables 1 and 2, Figures 3 and 4). We have already demonstrated (Tables 1 & 2) that cytogenetics and age are closely related. The frequency of poor risk cytogenetics (e.g. t(9;22), t(8;14), HoTr and complex karyotype) was higher among older patients and fewer older patients had HeH. There was little change in the outcome of patients during the study period. Although there was a marginally increase in the OS at 5 years for patients aged 30 years and above the difference was not statistically significant (data not shown).

In order to determine whether the adverse affect of cytogenetics was independent of age we performed multivariate analysis. Due to the relatively small number of patients with both cytogenetic and outcome data (n=162), we were able to consider only three cytogenetic risk groups: t(9;22) – all patients with t(9;22)/*BCR-ABL*; poor – patients with t(4;11), t(8;14), t(14;18), HoTr and complex karyotype; standard – all other patients. A Cox proportional hazards model containing just age and cytogenetic risk group indicated a statistical interaction between age and cytogenetics. Adding an interaction term to the model revealed that both age and cytogenetics were contributing significantly to outcome. Patients with t(9;22) had a 12.5 fold increase risk of dying (hazard ratio 12.50, 95% C.I. 2.69-58.07, p=0.001) while those with poor risk cytogenetics had a 3.5 fold increased risk (hazard ratio 3.47, 95% C.I. 1.45-8.37, p=0.007), both in comparison to patients with standard risk cytogenetics. The statistical interaction between cytogenetics and age indicates that the effect of cytogenetics might not be the same at all ages. However, given the size of the cohort, the relatively crude measure of outcome used and the heterogeneity of treatment it was not possible to investigate this further.

Incidence of major chromosomal abnormalities in this study compared to previously published data from clinical trials

We compared the incidence of the major chromosomal abnormalities in this study to that observed in six major clinical trials (Table 3). As most clinical trials impose age limits on potential subjects we restricted the comparison to those patients in this study aged between 15 and 59 year old. Aside from the variation in the incidence of normal karyotype and t(9;22) there was little difference. However, it should be noted that several of the abnormalities were only classified in a few studies. The overall frequency of t(9;22) in this population-based study was 15% which compares well with that reported by the two recent UK based trials: MRC UKALLXA[17] (11%) and UKALLXII[2] (16%). In contrast, the overall frequency of t(9;22) ALL reported by other trial based studies is much higher: ECOG2993[2] (25%); GMALL[19] (36%); GIMEMA0496[20] (23-31%); GFCH[21] (29%); SWOG9400[3] (27%); CALGB[22] (26%). (Table 4). These differences are likely to be due to a combination of factors, including the age profile of the underlying populations, recruitment bias and detection method. Although there are exceptions, generally studies with a lower frequency of t(9;22) comprise a greater proportion of younger patients and vice versa.

Discussion

We have reported the largest population-based cytogenetic study of adults with ALL. The overall incidence rate and pattern of incidence by age and gender was similar to that seen in other areas of the UK.[23] This was an appropriate region in which to examine the relationship between age and cytogenetics. Firstly, there was no overlap with the previous publication based on the MRC UKALLXII/ECOG 2993 cohort from which we derived our cytogenetic risk criteria. Although some patients (<10%) were treated according to the same protocol, they were not officially registered on the trial. Secondly, the age-specific OS rates observed in this region were similar to that observed in other regions of the UK.[4,24] The results clearly demonstrate that the incidence of cytogenetic and immunophenotypic subgroups varies markedly with the age. While it is known that the incidence of specific chromosomal abnormalities differs between children and adults, the age-specific frequency of such lesions within adult ALL, especially among those over 60 years old, was hitherto unknown or poorly studied.

The results of recent clinical trials of adult ALL have highlighted the importance of cytogenetics in predicting the risk of relapse.[2,3] Such studies support the development of cytogenetic-based risk stratification of adults in future trials. One of the limitations of

these studies was that they were based on a relatively small proportion of the total available patients; as most adult patients with ALL are not recruited to clinical trials. One of the key questions in this field of research is whether the specific chromosomal abnormalities identified as being indicators of poor outcome in the MRC UKALLXII/ECOG2993 trial retained their prognostic relevance outside the context of a clinical trial. Our analyses suggest that both age and cytogenetics are important predictors of outcome in adult ALL. The relatively small number of patients with individual poor risk chromosomal abnormalities prevented an in depth analysis. Overall the data in this study support our previous observations that patients with t(4;11), t(8;14), HoTr and complex karyotype have an inferior outcome. However, it should be noted that (a) there was evidence to suggest that the effect of cytogenetics varied with age; and (b) the treatment received by this cohort was over a 19 year period and hence heterogeneous.

We confirmed the findings of Burmeister et al (2008)[19] who reported that the frequency of t(9;22)/*BCR-ABL* positive adult ALL does not continue to increase beyond the fourth decade of life. These results are in contrast to the popularly held belief that the incidence of t(9;22) positive ALL continues to rise with age. The overall frequency of t(9;22) ALL in this study and other UK trial studies was considerably lower than that observed in series from other countries (Table 4). Although differences in the age profile of the underlying populations are likely to explain some of the variation, the picture appears more complicated and may reflect geographical heterogeneity.[25] Patients with t(9;22) are now usually treated with imatinib mesylate or another tyrosine kinase inhibitor in combination with multi-agent chemotherapy. These data indicate that such therapy will be suitable for a smaller fraction of patients aged more than 60 years than had been anticipated.

Even though this study is the largest and most comprehensive of its kind to date, it does have its limitations. Firstly, the number of patients was still quite small and hence the number with specific chromosomal abnormalities was too few to undertake detailed survival analysis. Secondly, rarer and secondary chromosomal abnormalities could not be considered. Thirdly, even though most treatment occurred in a single centre and with the same ethos, this study spanned nearly 20 years. Finally, the global genomic analysis of childhood ALL has revealed a wide spectrum of copy number alterations (CNA) beyond the resolution of cytogenetics.[26] Many are microdeletions targeting B-cell development genes (e.g. *IKZF1*, *PAX5*, *VpreB1* etc) and most correlate with established cytogenetic subgroups.[26,27] Initial investigations in adult ALL suggest that similar CNAs are present.[28] Given that approximately a half of the patients in this study could not be assigned to a clinically relevant cytogenetic subgroup future studies will need to incorporate high

quality cytogenetic, FISH and genomic data in order to fully characterise patients. Moreover, such studies will need to be population based in order to efficiently plan services, design clinical trials and fully utilise the prognostic relevance of genetic markers.

Several recent studies have reported that adolescents and young adults (AYA) have a better outcome when treated on paediatric protocols.[7-10] Several groups worldwide are now treating AYA up to the age of 29 years on paediatric protocols.[10,29] Since AYA are much less likely to enrol on clinical trials than children,[4] this study is the most informative to date as to their cytogenetic profile. Interestingly it is markedly different from both the classical paediatric profile and the adult profile.[1] The frequency of HeH is much lower than seen among childhood cohorts (13% v ~30%) whereas the frequency of t(9;22) and other "adult" cytogenetic abnormalities such as HoTr and complex karyotype is much lower. Unfortunately, our patients have not been screened for *ETV6-RUNX1* fusion. However, our previous study suggested that this would be present at a much lower frequency than in childhood ALL.[30] The frequency of T-ALL is this age group is noteworthy; at 25% it is higher than in both childhood ALL and adults aged over 30 years.

One of the major strengths of this study is the unselected nature of the cohort and we were able to estimate the incidence of ALL at all ages, and by gender and year of diagnosis. There was no evidence to suggest that the incidence of this disease was increasing with time. However, the observation that the incidence continues to increase with age among both males and females suggests that the absolute number of patients is likely to increase in the context of an aging population. Thus "elderly" ALL is likely to become an increasing health burden over the next two decades, especially as other have reported that there has been no improvement in outcome for these patients.[6] Hence new clinical trials targeting this age group are urgently required.

We were able to examine the cytogenetic profile of 124 patients aged over 60 years. This age group is largely under-reported due to the upper age limit of most clinical trials being 55-65 years. Although diagnostic cytogenetic investigations were less frequently requested in this age group, when they were attempted the success and abnormality rates were similar, if not better, compared to younger patients. These results suggest that pre-treatment cytogenetic analysis for adults with ALL should be performed irrespective of age. Interestingly the biological and cytogenetic profile of these "older" patients was quite different compared to younger patients. Mature-B ALL [plus t(8;14)/t(14;18)] was more prevalent while T-ALL was markedly less prevalent. Such

information is important for planning services and designing clinical trials. Patients with mature-B ALL will now routinely receive treatment on lymphoma protocols.[31] The translocations, t(4;11) and t(1;19), were rare among patients over 60 years old as was HeH. In contrast, the recently established poor risk groups – HoTr and complex karyotype – were more prevalent in this older subgroup.

As older adults (60 years plus) were less likely to receive curative treatment, the proportion of such patients included in the multivariate model was lower. Hence it is difficult to assess the effect of cytogenetics in this age group. Recent data from SEER showed that this age group was the only one that has not benefited from recent improvements in survival.[6] Therefore, further investigation into the cytogenetics of this age group is urgently required in order to maximum the usefulness of future clinical trials aimed at this age group.

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Table 1: Demographic, clinical and cytogenetic features of 349 adults with acute lymphoblastic leukaemia (ALL).

		15- 29	30-59	60+	Total
Total (n)		115	110	124	349
Gender	Sex Ratio M:F	1:0.6	1:1.1	1:1.1	1:0.9
WCC†	<10	55 (48%)	40 (38%)	42 (41%)	137 (43%)
	10 - 49.9	35 (30%)	33 (32%)	46 (45%)	114 (36%)
	50+	24 (21%)	31 (30%)	14 (14%)	69 (21%)
Immunophenotype*	Pro-B	7 (7%)	15 (15%)	11 (12%)	33 (10%)
	B-Cell Precursor	71 (68%)	60 (59%)	44 (49%)	175 (55%)
	Mature B	1 (<1%)	10 (10%)	21 (23%)	32 (10%)
	T-ALL	26 (25%)	11 (11%)	5 (6%)	42 (13%)
	Biphenotypic	0	6 (6%)	9 (10%)	15 (5%)
Cytogenetic Investigations	Attempted	98 (85%)	100 (91%)	94 (73%)	292 (84%)
	Successful	77 (79%)	79 (79%)	80 (85%)	236 (81%)
	Normal	25 (32%)	19 (24%)	18 (23%)	62 (26%)
	Abnormal	52 (68%)	60 (76%)	62 (77%)	174 (74%)
Cytogenetic Investigations (Pre Jan 1993)	Attempted	44 (76%)	51 (86%)	37 (61%)	132 (74%)
	Successful	32 (73%)	38 (75%)	30 (81%)	100 (76%)
	Normal	12 (38%)	8 (21%)	11 (37%)	31 (31%)
	Abnormal	20 (63%)	30 (79%)	19 (63%)	69 (69%)
Cytogenetic Investigations (Post Jan 1993)	Attempted	54 (95%)	49 (96%)	57 (90%)	160 (94%)
	Successful	45 (88%)	41 (84%)	50 (88%)	136 (85%)
	Normal	13 (29%)	11 (27%)	7 (14%)	31 (23%)
	Abnormal	32 (71%)	30 (73%)	43 (86%)	105 (77%)
Chromosomal Abnormality[e]	Classifications				
	Total	77	79	80	236
	t(9;22)(q34;q11)	6 (8%)	16 (20%)	14 (18%)	36 (15%)
	t(4;11)(q21;q23)	4 (5%)	5 (6%)	1 (1%)	10 (4%)
	t(1;19)(q23;p13)	4 (5%)	2 (3%)	0	6 (3%)
	t(8;14)(q24;q32)	0	7 (9%)	10 (13%)	17 (7%)
	t(14;18)(q32;q21)‡	0	2 (3%)	8 (10%)	10 (4%)
	HeH[a]	10 (13%)	4 (5%)	3 (4%)	17 (7%)
	HoTr[b]	1 (1%)	2 (3%)	4 (5%)	7 (3%)
	Complex[c]	2 (3%)	4 (6%)	9 (11%)	15 (7%)
	Other	25 (32%)	18 (23%)	16 (20%)	59 (25%)
	Normal[d]	25 (32%)	19 (24%)	18 (23%)	62 (26%)
CR rate**		89% (99/111)	77% (75/97)	51% (20/39)	79% (194/247)
OS Estimate – 5 yrs***		45%	19%	12%	30%
95% CI		35 – 55%	11 – 28%	4 – 27%	24-36%

† Information only available for 320 patients.

* Information only available for 297 patients.

‡ This karyotype was expressed in conjunction with the t(8;14) in 3 patients.

** CR only available for 247 patients.

*** OS rate available for 234 patients due to missing data.

[a] High hyperdiploidy (51-65 chromosomes).

[b] Low hyperdiploidy (30-39 chromosomes) / Near triploidy (60-78 chromosomes).

[c] Complex karyotype defined as five or more chromosomal abnormalities in the absence of an established cytogenetic subgroup.

[d] 20 or more normal metaphases in the absence of any clonal chromosomal abnormality.

[e] Mutually exclusive.

Table 2: Demographic, clinical and survival data for 349 adults with acute lymphoblastic leukaemia (ALL).

	Total		Sex Ratio M:F	Age		WCC†		Outcome*							
								Treated		CR rate**		Deaths***		Overall Survival at 5yrs****	
				Mean	%>60 yrs	Median	%>50							Overall Survival	95% CI
Total (Full Dataset)	349		1:0.9	46.4	36%	13.6	20%	250	72%	194	79%	177	73%	30%	(24–36%)
Successful Cytogenetics															
Total	236		1:0.8	45.4	34%	14.6	20%	177	75%	133	75%	126	71%	29%	(22 – 37%)
t(9;22)(q34;q11)	36	(15%)	1:0.6	50.6	39%	30.1	42%	26	72%	17	65%	24	92%	9%	(2 – 26%)
t(4;11)(q21;q23)	10	(4%)	1:1.5	39.1	10%	43.6	50%	9	90%	7	78%	6	67%	33% at 3yrs	(8-62%)
t(1;19)(q23;p13)	6	(3%)	1:5	33.2		21.5	16%	6	100%	6	100%	3	50%	60%	(13 – 88%)
t(8;14)(q24;q32)	17	(7%)	1:0.9	60.8	59%	15.7	6%	10	59%	4	44%	8	80%	20%	(3 – 48%)
t(14;18)(q32;q21)‡	10	(4%)	1:0.8	60.0	67%	20.0	16%	5	50%	2	40%	4	80%	33% at 1yr	(1-77%)
HeH[a]	17	(7%)	1:0.5	33.9	18%	3.1	6%	15	88%	15	100%	5	36%	77%	(45 – 92%)
HoTr[b]	7	(3%)	1:1.3	55.1	86%	2.6	-	6	86%	4	67%	6	100%	0%	-
Complex[c]	15	(7%)	1:0.5	58.9	60%	13.0	-	5	33%	4	80%	4	80%	20%	(1 – 58%)
Other	59	(25%)	1:0.8	42.2	29%	16.3	24%	48	85%	39	81%	34	76%	27%	(14 - 41%)
Normal[d]	62	(26%)	1:0.7	40.8	29%	10.0	16%	49	79%	35	71%	34	69%	32%	(18- 46%)
Cytogenetic Risk Group															
t(9;22)	36	15%	1:0.6	50.6	39%	30.1	42%	26	72%	17	65%	24	92%	9%	(2-26%)
Poor	56	24%	1:1.3	55.8	52%	15.2	13%	33	59%	21	66%	26	79%	19%	(7-36%)
Standard	144	61%	1:0.8	40.0	26%	11.0	18%	118	82%	95	82%	76	67%	37%	27-46%)

† Information only available for 320 patients.

* This only includes those 250 patients treated with curative intent.

** CR only available for 247 patients.

*** Status unavailable for 16 patients.

**** OS information available for 234 patients due to missing data.

‡ This karyotype was expressed in conjunction with the t(8;14) in 3 patients

[a] High hyperdiploidy (51-65 chromosomes).

[b] Low hyperdiploidy (30-39 chromosomes) / Near triploidy (60-78 chromosomes).

[c] Complex karyotype defined as five or more chromosomal abnormalities in the absence of an established cytogenetic subgroup.

[d] 20 or more normal metaphases in the absence of any clonal chromosomal abnormality.

Table 3: Incidence of major chromosomal abnormalities other than t(9;22) in adult ALL observed in this study compared to previously published clinical trials.

Study	Reference	No. patients tested	t(9;22) %	t(4;11) %	t(1;19) %	t(8;14) %	t(14;18) %	HeH[a] %	HoTr[b] %	Complex[c] %	Normal[d] %
This study (15-59 year olds only)	NA	236	14%	6%	4%	4%	1%	9%	2%	4%	29%
MRC UKALLXA	17	350	11%	3%	3%	NA	NA	8%	NA	NA	34%
UKALLXII/ECOG 2993	2	1373	19%	4%	2%	1%	NA	6%	2%	3%	14%
CALGB	22	256	26%	5%	NA	NA	NA	NA	NA	NA	25%
GIMEMA 0496	20	386	26%	7%	2%	NA	NA	NA	NA	NA	26%
SWOG 9400	3	140	26%	5%	5%	NA	NA	NA	NA	NA	22%
GFCH	21	443	29%	4%	3%	5%	NA	7%	NA	NA	15%

NA, Not available.

[a] High hyperdiploidy (51-65 chromosomes).

[b] Low hyperdiploidy (30-39 chromosomes) / Near triploidy (60-78 chromosomes).

[c] Complex karyotype defined as five or more chromosomal abnormalities in the absence of an established cytogenetic subgroup.

[d] 20 or more normal metaphases in the absence of any clonal chromosomal abnormality.

Table 4: The incidence of t(9;22) in adult ALL in different studies by age.

Study	Reference	No. patients tested	t(9;22) n (%)	Detection Method	Age Range (yrs)	Mean Age (yrs)	<20years n (%)	<30 years n (%)
MRC UKALLXA	17	350	40 (11%)	Cytogenetics	15-60+	NA	115 (33%)	186 (53%)
This study	NA	236	36 (15%)	Cytogenetics, (plus some FISH and RT-PCR	15-91	45	42 (18%)	77 (33%)
UKALLXII	2	872	142 (16%)	Cytogenetics, FISH and RT-PCR	15-55	31	207 (24%)	453 (52%)
ECOG2993	2	501	125 (25%)	Cytogenetics, FISH and RT-PCR	15-65	36	61 (12%)	190 (38%)
CALGB	22	256	67 (26%)	Cytogenetics	15-60+	33	NA	109 (43%)
GIMEMA 0496	20	386	102 (26%)	Cytogenetics and RT-PCR	15-60	31	NA	148 (46%)
SWOG 9400	3	140	36 (26%)	Cytogenetics and RT-PCR	15-65	32	NA	86 (43%) Based on all 200 patients
GFCH	21	443	127 (29%)	Cytogenetics	15-60+	37	90 (20%)	169 (38%)
GMALL	19	2498	904 (36%)	RT-PCR	15-74	NA	<25 yrs 481 (19%)	<35 yrs 902 (36%)

Fig.1. Number of patients diagnosed in the North East of England with adult acute lymphoblastic leukaemia between 1983 and 2001 sub-divided by cytogenetic analysis at diagnosis

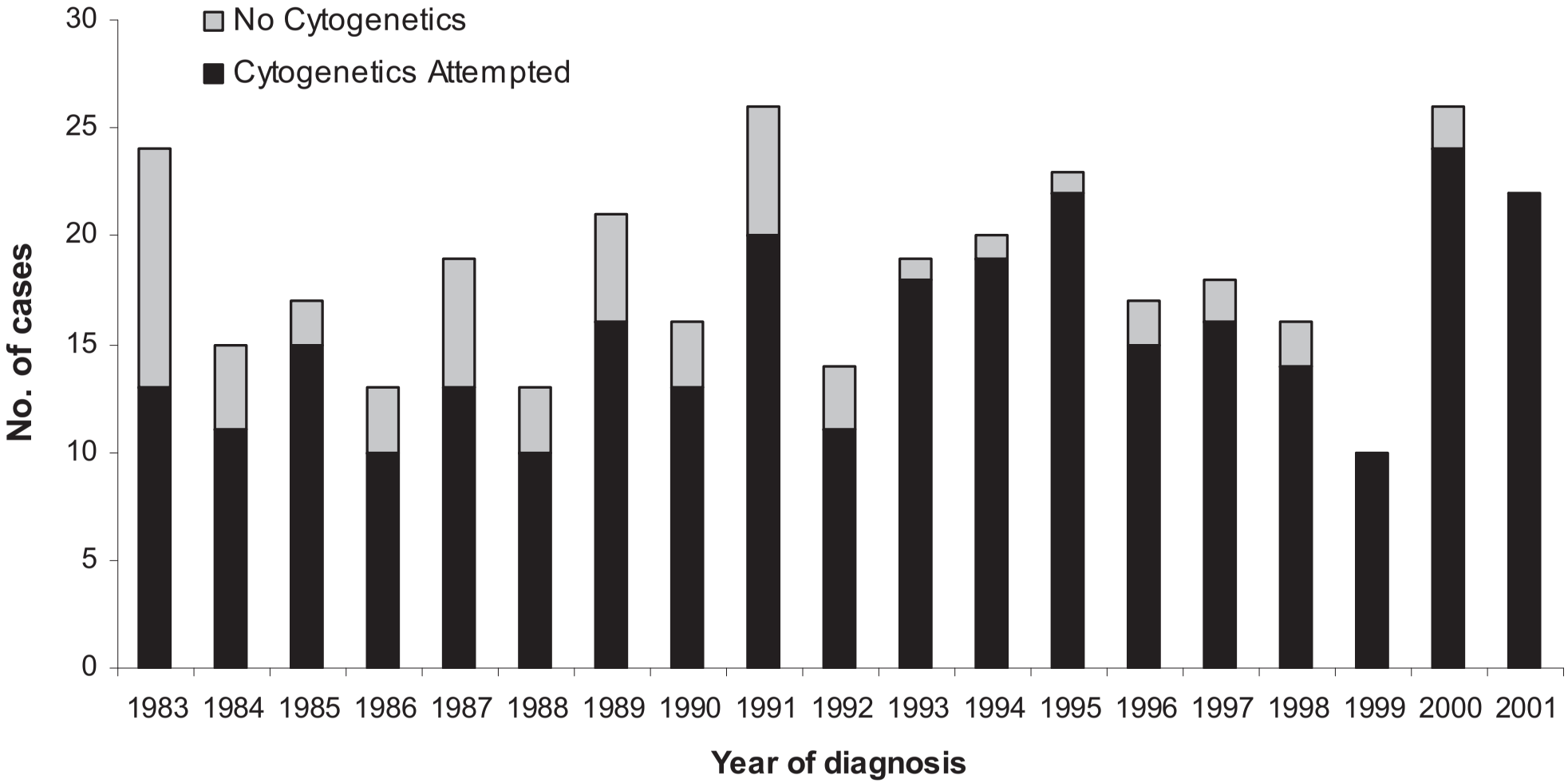
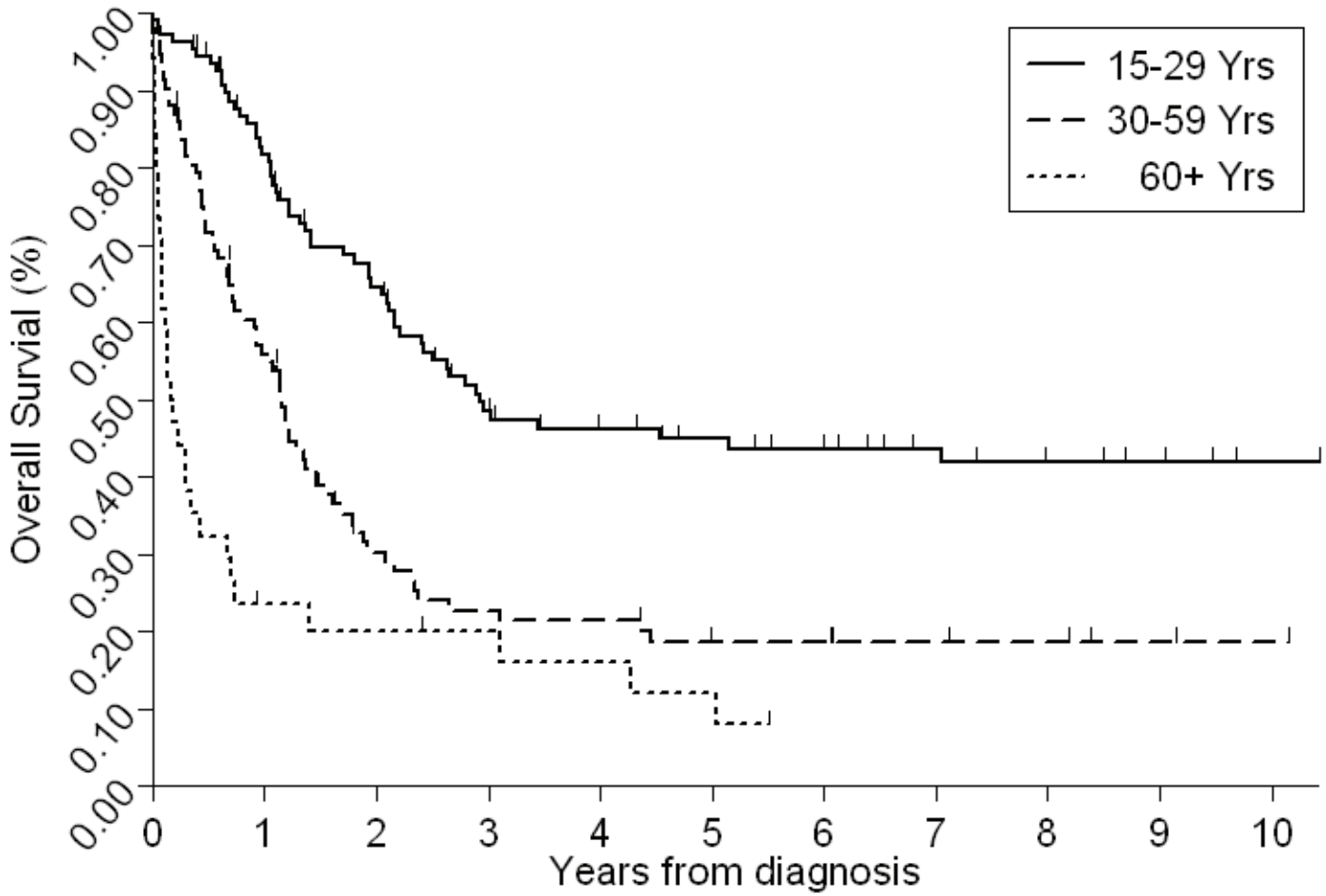


Fig.2. Age-specific incidence of adults with acute lymphoblastic leukaemia (ALL) in the North East of England by sex.

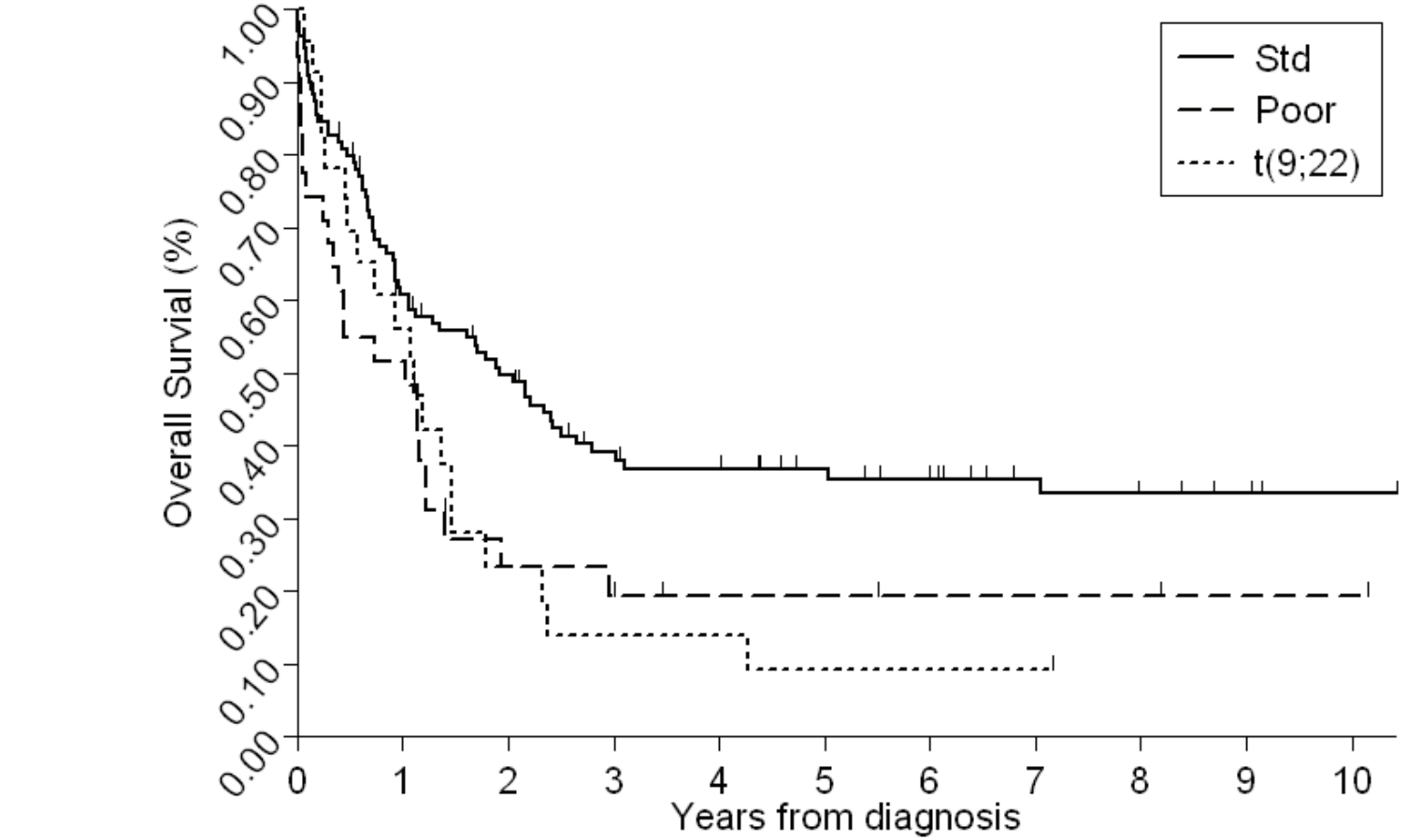
Fig.3. Overall survival of adults with acute lymphoblastic leukaemia (ALL) by age at diagnosis



Number at risk

15-29 Yrs	108	83	63	44	38	34	30	26	23	21	18
30-59 Yrs	92	50	24	18	17	13	13	11	10	8	7
60+ Yrs	34	7	6	5	4	3	1	1	1	1	1

Fig 4. Overall survival of adults with acute lymphoblastic leukaemia (ALL) by cytogenetic risk group



Number at risk

Std	110	63	49	35	32	27	23	18	16	14	12
Poor	31	16	6	5	3	3	2	2	2	1	1
t(9;22)	23	12	5	3	3	2	2	2	1	1	1