The prognostic impact of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: Results from the MRC ALL97/99 randomised trial.

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ABSTRACT

Background

Chromosomal abnormalities in childhood acute lymphoblastic leukaemia are well established disease markers and indicators of outcomes. However, the long term prognosis and independent prognostic effect of some abnormalities has been questioned. Also less is known about the relationship between cytogenetics and the characteristics of relapse (time and site of relapse) known to predict outcome post-relapse.

Patients and Methods

We analysed cytogenetic data from 1725 children with B-cell precursor acute lymphoblastic leukaemia treated on MRC ALL97; with a median follow-up time of 8.2 years. Univariate and multivariate analysis were used to examine the risk of relapse, event free and overall survival of 21 individual chromosomal abnormalities and three cytogenetic risk groups.

Findings

Analysis showed that two chromosomal abnormalities were associated with a significantly superior outcome whereas five were associated with an increased risk of relapse: *ETV6-RUNX1* – HR=0.51 (95% CI 0.38,0.70), High hyperdiploidy – 0.60 (0.47,0.78), iAMP21 – 6.04 (3.90,9.35), t(9;22) – 3.55 (2.21,5.72), *MLL* translocations – 2.98 (1.71,5.20), abnormal 17p – 2.09 (1.30,3.37) and loss of 13q – 1.87 (1.09,3.20). Multivariate analysis incorporating age, white cell count and treatment parameters revealed that six cytogenetic parameters (*ETV6-RUNX1*, high hyperdiploidy, iAMP21, t(9;22), loss of 13q and abnormal 17p) retained their significance for increased relapse risk. Based on these data, patients were classified into good, intermediate and poor cytogenetic risk groups. Slow early treatment response correlated with cytogenetic risk group: 34/460 (7%), 22/211 (10%) and 27/95 (28%) respectively ($p<0.0001$). In addition, the proportion suffering a very early (<18m) relapse varied by cytogenetic risk group: 8/129 (6%), 24/98 (25%) and 37/82 (45%) respectively ($p<0.0001$). However, there was no difference in the site of relapse by cytogenetic risk group.

Interpretation

Individual chromosomal abnormalities are strong independent indicators of outcome, especially risk of relapse. Diagnostic cytogenetics not only identifies patients with a higher rate of relapse but also those who are likely to suffer a "high risk" relapse.

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a heterogeneous disease at the cytogenetic and genetic levels.[1] Numerous acquired genetic abnormalities have been described in the bone marrow cells of patients with ALL; including chromosomal translocations, aneuploidy, deletions and amplifications. Several genetic aberrations are pathognomic of the disease and can be used to monitor the patient's response to therapy. Along with treatment regimen, age, white count cell (WCC) and minimal residual disease (MRD) detection, the genetic profile of the leukaemia is a major determinant of clinical outcome, especially the risk of relapse.[2] Improvements in the design and delivery of frontline protocols for paediatric ALL have increased survival rates steadily over the past four decades.[2] Despite these advances, 15%-20% of children with ALL will suffer a relapse.[3] The continued refinement and monitoring of prognostic factors is warranted to update risk stratification algorithms in the light of new discoveries and evaluate their role in the context of revised and developing protocols.

Recent studies have suggested that the strongest risk factors for survival after a first relapse are the length of the first remission and the site of relapse.[3] Several clinical study groups have proposed relapse risk classifications based on these factors along with immunophenotype.[3] Increasingly, these relapse risk groups are being used to direct post relapse therapy, especially the use of stem cell transplantation. However, there are no studies examining the association between cytogenetics and these relapse risk groups.

In this study, we present outcome data from the MRC ALL97/99 paediatric trial stratified by specific chromosomal abnormalities and cytogenetic risk group. In addition, we examine the relationship between presentation cytogenetics and relapse risk group.

PATIENTS AND METHODS

Study Population and treatment

Between April 1997 and June 2002, 1725 children with B-cell precursor ALL (BCP-ALL) and aged 1-18 years old were treated on the MRC ALL97 and ALL99 phases of the trial (Figure 1). Infants under the age of one year were not eligible for this trial. Centres obtained local ethical committee approval and written informed consent from patients or parents. Full treatment protocols and overall results have been published.[4-6] Both phases, ALL97 and ALL99, included a steroid and purine randomisation: prednisolone / dexamethasone and mercaptopurine / thioguanine in induction and maintenance. In ALL97, patients received a four drug induction followed by two or three intensification

blocks, appropriate CNS directed treatment and continuing therapy for a total of 2 years. High risk patients were identified by the Oxford Hazard Score (based on age, gender and white cell count (WCC)) or by the presence of t(9;22)(q34;q11.2)/*BCR-ABL1*, near haploidy (<30 chromosomes), low hypodiploidy (30-39 chromosomes) or *MLL*/11q23 translocations (under 2 years old) and were transferred to a more intensive protocol (HR1).[5] In ALL99, children were stratified on the basis of age and WCC to regimen A (<10 years and $<50x10^9$/L) or regimen B (all others). Patients received a three/four (regimen A/B) drug induction and were classified as a slow early responder (SER) if the day 15/8 (regimen A/B) marrow contained 25% blasts of higher. Patients who failed to remit, were SERs or had t(9;22), near haploidy, low hypodiploidy or *MLL*/11q23 translocations (under 2 years old) were transferred to the more intensive regimen C. After induction, patients received consolidation, two interim maintenance blocks, two delayed intensification blocks and continuing therapy for up to 2 years (girls) or 3 years (boys). All patients treated on HR-1 were eligible for CR1 sibling allogeneic transplantation but only failure to achieve remission at day 29 and presence of t(9;22)(q34;q11.2)/*BCR-ABL1* were indications in ALL99.

Cytogenetics

Cytogenetic analyses were performed on the pre-treatment bone marrow or blood samples of 1694/1725 (98%) patients by member laboratories of the UK Cancer Cytogenetics Group (UKCCG) (n=30) whose satisfactory performance was monitored by a national external quality assurance scheme: UK National External Quality Assessment Service (NEQAS) for Clinical Cytogenetics.[7] The results were collected centrally by the Leukaemia Research Cytogenetics Research Group (LRCG).[8] Karyotypes were not routinely analyzed centrally, but were reviewed for accuracy in description of the structural and numerical, clonal chromosomal abnormalities, which were reported in accordance with the International System for Human Cytogenetic Nomenclature (ISCN).[9] Analysis of fewer than 20 normal metaphases was classified as a failure, which occurred in 275/1694 (16%) cases. A normal karyotype (20 or more normal metaphases) was present in 219/1419 (15%) cases. A clonal abnormality was detected in 1200/1419 (85%) cases. Fluorescence in situ hybridisation (FISH) testing was performed locally or centrally by the LRCG as previously described.[10] FISH for *ETV6-RUNX1*, *BCR-ABL1* and *MLL* was performed on 1451 (84%), 1448 (84%) and 1431 (83%) respectively, using commercial fusion or break-apart probes as previously described.[10] The Multiprobe-I system for the detection of aneuploidy was performed on 265 (15%) cases with failed or incomplete cytogenetics or a normal karyotype. Each patient was classified according to whether each chromosomal abnormality was present, absent or had not been

appropriately tested. Chromosomal abnormalities were classified as primary or secondary based on prior knowledge.[1] Analysis of secondary abnormalities was restricted to those that were present in 10 or more cases.

Statistics and Endpoints

Event free survival (EFS) and overall survival (OS) were defined as the time from the start of treatment to relapse/death and death, respectively. Relapse free survival (RFS) was calculated only for patients who achieved a complete remission and was defined as the time from the date of complete remission until relapse; with deaths in first remission being censored. Patients without an event of interest were censored at the date of last contact or date of second neoplasm whichever was earlier. A second neoplasm was diagnosed in 11 (<1%) patients. RFS, EFS and OS survival estimates were calculated using the Kaplan-Meier method. Hazard ratios comparing RFS, EFS and OS between subgroups were calculated using univariate Cox models. Multivariate Cox regression modelling was performed for RFS, EFS and OS using a forward-selection stepwise modelling process; the difference in the log likelihood (-2*LogLikelihood) was used along with an adjustment for steroid randomisation (dexamethasone versus prednisolone) and phase of trial (ALL99 versus ALL97). Age and a log transformed WCC factor were modelled as continuous variables, while all other factors were categorical variables. All variables in the model were linear and conformed to the proportional hazards assumption. Interaction between treatment protocol and cytogenetic parameters were explored by the addition of an interaction term in the final model and inspecting its effect on the log likelihood. Only the following cytogenetic variables were considered in the model – high hyperdiploidy (51-65 chromosomes), *ETV6-RUNX1*, *MLL* translocations, iAMP21, t(9;22), abnormal 17p and loss of 13q. Not all cases were screened for all possible abnormalities (see cytogenetics paragraph above). As complete data is required to include a case in the model, we adopted two strategies - imputing missing values and reducing the dataset to cases with complete information. We performed both methods as each has implications in terms of bias. The results obtained were very similar. We opted to present the results from the "imputed" analysis because they were based on a larger number of cases and hence generated more precise estimates. Among the 1546 cases used for the modelling, 1233 (80%) had complete information. Imputing was based on the assumption of mutual exclusivity, which is supported by the data in Supplementary Table 1. Thus cases with one primary chromosomal abnormality were classified as negative for the presence of other primary chromosomal abnormalities. The number of cases imputed as absent were: high hyperdiploidy (n=79); *ETV6-RUNX1* (n=188); t(9;22) (n=5); iAMP21 (n=219); *MLL* translocations (n=9). In addition, 127 cases with

failed cytogenetics were classified as negative for abnormal 17p and loss of 13q. While a more stringent multiple comparisons adjustment might be applicable in a classical setting, because of the investigative nature of this analysis, all tests were conducted at the 1% significance level. All analyses were performed using Intercooled Stata 11.0 for Windows (Stata Corporation, College Station, Texas, USA).*Role of the funding source*

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

RESULTS

Survival estimates for the whole cohort of 1725 patients at 5 years were: RFS 81% (79-83%); EFS 78% (95% CI 76-80%); and OS 87% (86-89%) after a median follow-up time of 8.2, 8.3 and 8.4 years respectively. In total there were 351 (20%) relapses, 16 (1%) non-remitters and 257 (15%) deaths including 57 (3%) in first remission. Patients treated on the ALL99 phase of the trial had a significantly improved outcome compared to those treated on the ALL97 phase: RFS 84% (81-87%) v 78% (75-81%) (p=0.003); EFS 81% (78-83%) v 75% (72-78%) (p=0.005); OS 90% (87-91%) v 85% (83-88%) (p=0.014).

On the basis of cytogenetic and FISH data 1269/1694 (75%) cases were assigned to the cytogenetic subgroups under consideration. Cases were assigned to one (n=983, 78%), two (n=228, 18%), three (n=53, 4%) or four (n=5, <1%) of the cytogenetic subgroups listed in Table 1. Among the remaining 425 (25%) cases, 152 (9%) had some other chromosomal abnormality, 131 (8%) had a normal karyotype and 142 (8%) did not achieve a cytogenetic result. With the exception of seven cases where t(9;22) or *ETV6-RUNX1* was observed in a high hyperdiploid (51-65 chromosomes) karyotype, primary chromosomal abnormalities did not co-exist in the same karyotype (Supplementary Table 1). In contrast, secondary abnormalities occurred together frequently and often in a non-random pattern.

There was no significant variation in the ratio of boys to girls by chromosomal abnormality (Supplementary Table 2). Low hypodiploidy (30-39 chromosomes), iAMP21, *IGH-CEBP*, abnormal 9p and abnormal 17p were associated with older age. Patients with t(1;19)(q23;p13), t(9;22), *MLL* translocations, near haploidy (<30 chromosomes) and

abnormal 9p had higher WCCs at presentation whereas high hyperdiploid patients had lower WCCs.

Table 1, Figure 2, supplementary table 3 and supplementary figures 1 and 2 describe the outcome of patients with different chromosomal abnormalities. There was little correlation between cytogenetics and failure to achieve a remission or death in first remission; six of the seven t(9;22) patients who died in first remission underwent bone marrow transplantation. *ETV6-RUNX1* and high hyperdiploidy were associated with an improved outcome whereas t(9;22), iAMP21, *MLL* translocations, near haploidy, low hypodiploidy, t(17;19)(q23;p13), abnormal 17p and loss of 13q were associated with a higher risk of relapse and/or death. There were too few patients with an *IGH-CEPB* or *IGH–ID4* fusion to assess their prognosis accurately.

Among the 50 patients with abnormal 17p, 27 (54%) also had high hyperdiploidy (n=21) or *ETV6-RUNX1* (n=6) (Supplementary Table 1). Abnormalities included i(17q) (n=17), del(17p) (n=7), der/dic(17p) (n=11), add(17p) (n=8) and -17 (n=7). At least 42 (84%) of these 17p abnormalities resulted in loss of 17p13. The presence of abnormal 17p among patients with *ETV6-RUNX1* or high hyperdiploidy did not adversely affect their relapse risk (HR=1.69, 95% CI 0.74-3.85, p=0.210), whereas for patients without *ETV6-RUNX1* or high hyperdiploidy the presence of an abnormal 17p conferred a three-fold increased risk of relapse (HR=3.17, 95% CI 1.76-5.74, p=0.0001). Given this difference and knowing that i(17q) correlates with high hyperdiploidy[1], we examined the type of 17p abnormality across cytogenetics subgroups. We saw some evidence of the high hyperdiploidy-i(17q) association [11/21 (52%) v 6/29 (21%), p=0.03] but did not observe any other relationship which might explain the differential effect of abnormal 17p.

A total of 44 patients had either a del(13q) (n=27), monosomy 13 (n=16) or both (n=1). These abnormalities were clearly secondary and frequently (24/44, 55%) coexisted with a known primary abnormality, particularly *ETV6-RUNX1* (n=11), high hyperdiploidy (n=5) and t(1;19) (n=5) (Supplementary Table 2). There was no correlation between del(13q)/-13 and cytogenetic subgroup. Among 22 patients with a deletion and defined breakpoints, 16 (73%) involved 13q14. As with abnormal 17p, the effect of loss of 13q within the *ETV6-RUNX1* and high hyperdiploid groups was not significant (HR=1.46, 95% CI 0.46-4.60, p=0.518). Although the effect of 13q loss among patients with other abnormalities was consistent with an increased relapse risk it was not significant (HR=1.78, 95% CI 0.94-3.39, p=0.078).

Previous studies have found triple trisomy (TT) (+4, +10, +17)[11] or trisomy 18 (+18)[12] to be associated with an improved outcome. In this study, 419/562 (75%) and 484/562 (86%) cases could be accurately classified by TT and +18 status, respectively. Only 253/409 (62%) cases that were classified by both criteria were concordant (i.e. TT and +18 (n=190), or neither (n=63)), suggesting the criteria do not identify exactly the same patient populations. There was no difference in outcome by TT status (HR=0.80, 95% CI 0.49-1.33, p=0.395) (Supplementary Figure 3). However, high hyperdiploid patients with +18 had a reduced risk of relapse compared to those with two copies of chromosome 18 (HR=0.44, 95% CI 0.26-0.74, p=0.002). As there was an overlap in the patient cohort between this and our previous study,[12] we repeated the analysis after excluding patients treated on the ALL97 phase. The result was nearly identical (HR=0.37, 95% CI 0.18-0.76, p=0.006).

A multivariate Cox proportion hazards model was used to assess the significance of each cytogenetic abnormality that had been found to be significant in univariate analysis within the context of other risk factors. Table 2 and Supplementary Tables 3 and 4 show that six cytogenetic variables (iAMP21, t(9;22), *ETV6-RUNX1*, loss of 13q, abnormal 17p and high hyperdiploidy) retained their significance in the RFS and EFS models and five (iAMP21, t(9;22), *ETV6-RUNX1*, abnormal 17p and high hyperdiploidy) in the OS model. *MLL* translocations did not retain their prognostic significance in any of the models. There was no statistical interaction between *ETV6-RUNX1* or high hyperdiploidy and the phase of trial (ALL97 versus ALL99) in the RFS, EFS or OS multivariate models. Individual poor risk chromosomal abnormalities were too rare to test for interaction reliably.

The *MLL* subgroup was heterogeneous cytogenetically and comprised patients with t(4;11)(q21;q23)/*MLL-AF4* (n=17), t(9;11)(p21~2;q23)/*MLL-AF9* (n=5), t(11;19)(q23;p13)/*MLL-ENL* (n=1), t(10;11)(p12~14;q23)/*MLL-AF10* (n=1) and unknown *MLL* partners (n=6). Patients with t(4;11) (n=17) were significantly older (median age 8.6 v 1.6 years, p=0.002) compared to other *MLL* patients (n=13), but there was no difference with respect to sex or WCC (data not shown). Most *MLL* patients had a common or pre-B immunophenotype (18/29, 62%), including seven t(4;11) patients. The remaining 11 (38%) patients (9 t(4;11), 1 t(11;19) and 1 unknown *MLL* partner) had a null or pro-B immunophenotype. As the median age of patients with a *MLL* translocation was 4 years, we examined the prognostic effect of *MLL* status among younger and older patients. Among patients under the age of 4 years, the presence of a *MLL* translocation was associated with a higher risk of relapse (HR=8.75 (95% CI 4.55, 16.84), p<0.0001) but this was not the case among patients over 4 years old (HR=0.91 (0.29, 2.83), p=0.865). Due to the strong correlation between t(4;11) and age in this

cohort, similar risks were observed when examining the risk of relapse associated with t(4;11) and other *MLL* translocations: HR=1.37 (0.51,3.68), p=0.529 and HR=5.94 (3.06,11.52), p=0.0001, respectively.

We classified 1547 patients hierarchically into three cytogenetic risk groups (Table 3). There was no significant difference in RFS, EFS or OS between the 1547 patients classified into these three cytogenetic risk groups and the 178 patients who could not be evaluated due to failed or missing cytogenetic data (supplementary table 3). We used outcome data from this study to derive this classification but there were exceptions. The decision to classify near haploidy, low hypodiploidy and t(17;19) as poor risk despite not being able to formally test these groups, is supported by the fact that the low EFS/OS observed is consistent with several previous studies[1] and both near haploidy and low hypodiploidy were included in the trial risk stratification algorithm as high risk features. The *MLL* translocation group was included in the poor risk group despite not retaining its significance in the multivariate model because the univariate analysis was clearly significant and patients under the age of 2 years with a *MLL* translocation were treated as high risk in this trial. This, and other high risk criteria, meant that 18/30 (60%) patients with a *MLL* translocation were treated on HR1 or Regimen C. Poor risk abnormalities correlated with older age and higher WCC (Supplementary Table 2). Tables 1, 2 and 3, Supplementary Tables 3, 4 and 5, Figure 2 and Supplementary Figure 1 and 2 illustrate the strong correlation between cytogenetic risk group and outcome both in univariate and multivariate analysis. There was no statistical interaction between cytogenetic risk group and the phase of trial (ALL97 versus ALL99) in the RFS, EFS or OS multivariate models.

Among 766 ALL99 patients who were assessed for early response and could be classified into a cytogenetic risk group, 83 (11%) patients were slow early responders (SER). SER percentage varied significantly by cytogenetic risk group: good 34/460 (7%), intermediate 22/211 (10%) and poor 27/95 (28%) (p<0.0001).

We used this classification to examine the relationship between cytogenetics and relapse characteristics (Table 4). There was a strong correlation between cytogenetic risk group and the time to relapse. Patients in the poor cytogenetic risk group were more likely to relapse within 18 months of diagnosis, whereas those in the good cytogenetic risk group were more likely to have later, off-treatment, relapses (p<0.0001). However, there was no correlation between the site of relapse and cytogenetic risk group whether divided by individual sites (as in Table 4) or dichotomously according to marrow involvement (data not shown). Finally, we examined the relationship between cytogenetic risk group and relapse risk group, as used previously by us, to examine survival after relapse in the

UKALLR2 trial.[13] Table 3 shows that relapses arising from the poor cytogenetic risk group were five times more likely to be classified as a high risk relapse compared to those occurring in the good cytogenetic risk group ($p<0.0001$).

DISCUSSION

This dataset represents one of the largest and most comprehensive cytogenetic studies of childhood ALL yet published. The results provide compelling evidence for the prognostic significance of cytogenetics in this disease. As ALL99 patients fared better than their ALL97 counterparts, we assessed whether there was any interaction between cytogenetic parameters and protocol. No statistical interaction was observed suggesting that the improved outcome seen in ALL99 benefitted all patients irrespective of cytogenetic risk group. We have verified conclusively the excellent prognosis associated with *ETV6-RUNX1* fusion and high hyperdiploidy.[12, 14-16] Multivariate analyses confirms that these associations are independent of other risk factors. Moreover, contrary to reports from several other groups we did not observe any increased risk of late relapses associated with *ETV6-RUNX1*.[17-19] The crude relapse rate in our study for *ETV6-RUNX1* patients was substantially lower, suggesting our treatment protocol might be averting the late relapses seen, for example, in the NOPHO study.[17]

Outcome heterogeneity in high hyperdiploidy by specific trisomies has been debated for many years.[1] We could not confirm the results of the Children's Oncology Group study suggesting that high hyperdiploid patients with TT (+4,+10,+17) have a superior outcome.[11] Rather, this analysis confirms our previous findings regarding the favourable outcome of high hyperdiploid patients with +18.[12] There are a number of differences between the two studies which may account for this discrepancy. Firstly, the Children's Oncology Group analysis was not restricted to high hyperdiploid patients and thus their "non triple trisomy" group included patients with other abnormal and normal karyotypes. While this approach includes very rare non-high hyperdiploid cases with TT, it introduces substantial heterogeneity into the analysis making the results more difficult to interpret. In contrast, our analysis represents simple comparison within the high hyperdiploid subgroup between patients with and without a triple trisomy. Secondly, although the Children's Oncology Group study comprised over 5000 patients, they were treated over a longer period of time (11 years) and in a different era (1988-1999). Thirdly, poor chromosome morphology results in incomplete classification rates and also chromosome misclassification; both of which are likely contributing factors. FISH screening will resolve

these two technical problems and future, more accurate datasets, will hopefully resolve this ongoing question.

This study has confirmed the poor outcome associated with t(9;22), near haploidy, low hypodiploidy, *MLL* translocations, t(17;19) and iAMP21,.[1] This was despite patients with the t(9;22), near haploidy, low hypodiploidy and *MLL* translocations (<2 years) receiving more intensive treatment. However, it should be noted that equivalent cytogenetic subgroups treated on the predecessor trial, UKALLXI, had an extremely poor outcome (near haploidy (EFS at 5 yrs 0%); t(4;11) (13%) and t(9;22) (27%))[20] suggesting that the risk stratification of these rare cytogenetic subgroups was beneficial. Although patients with a *MLL* translocation had an inferior outcome overall, there was clear evidence of outcome heterogeneity within this group. Our analysis suggests that both age and t(4;11) may be important factors. Due to the relatively small number of patients in this subgroup and the strong correlation between t(4;11) and age, we were not able to determine which factor is driving this heterogeneity. The situation is further confounded by the fact that 18/30 were treated as high risk either on the basis of a *MLL* translocation or other risk features. While it is clear from previous studies that age is an important prognostic factor for patients with *MLL* translocations, most have compared infants (<1 year) with children (>1 year) or just considered infants[21-23]; and our study did not include any infants. Heterogeneity of outcome by *MLL* partner, with t(4;11) and t(9;11) faring poorly, has also been suggested especially among children (>1 year old).[21, 22] In addition, a study from St Jude Children's Research Hospital reported a very good outcome for t(4;11) patients albeit on just a handful of cases.[16] This important clinical issue will need to be addressed using a larger cohort of children. However, a recent gene expression study which reported a link between differential expression of *HOXA* genes and outcome among infants with t(4;11)[24] raises the possibility that secondary genetic alterations could be responsible for this heterogeneity.

We found that patients with abn(17p) had a significantly inferior outcome and in particular a higher rate of relapse, but this finding was restricted to patients without one of the good risk abnormalities of *ETV6-RUNX1* and high hyperdiploidy. This finding mirrors the situation observed in AML, whereby the presence of poor risk cytogenetic abnormalities do not affect the good prognosis of patients with t(15;17), t(8;21) or inv(16).[25] We have recently reported that abn(17p)/-17 are independent adverse risk factors in AML.[25] Studies in childhood ALL have been limited to i(17q) within the high hyperdiploidy subgroup.[1] This study confirms our previous observations that abn(17p) does not negate the good prognosis associated with high hyperdiploidy.[12] In adult ALL, abn(17p) was not a risk factor in BCP-ALL but results in T-ALL were strongly suggestive

of an association with poor outcome.[26, 27] In AML, abnormalities of 17p correlate with complex karyotypes and p53 inactivation/mutation.[28] While p53 mutations are rare in childhood ALL, it has been suggested that they occur more frequently in high risk disease.[29] Independent studies are required to confirm these observations and unravel the nature of these aberrations.

In 2000, Heerema et al[30] reported that del(13q) was associated with an increased risk of relapse in childhood ALL, although the risk was not independent in multivariate analysis and did not extend to OS. We included patients with monosomy 13 in our analysis and found that the increased risk of relapse was independent of other risk factors although, again, OS was not affected. While it is tempting to speculate that the *RB1* gene is the target of this abnormality, this requires verification.

Historically several groups have reported that t(1;19) has an inferior outcome unless treated by more intensive treatment.[1] However, in this and our previous study, UKALLXI[20], patients with t(1;19) have always fared slightly but not significantly better than the average (Table 1). The St Jude Children's Research Hospital recently reported that t(1;19) patients have an increased risk of CNS relapse.[16, 31] Among our 50 t(1;19) patients, only 6 (12%) relapsed and 3 (50%) involved the CNS. However, with so few relapses occurring in this subgroup it is impossible to conclude that this rate is truly higher than the overall rate of 110/351 (31%).

The prognostic relevance of dic(9;20) is currently the subject of debate with several groups reporting association with other poor risk features and increased incidence in high risk cohorts.[32, 33] Our data, however, indicate no evidence for an increased risk of relapse or inferior outcome in this subgroup. This abnormality is both rare and heterogeneous at the molecular level[34]; these two factors make assigning a reliable prognosis to patients with dic(9;20) very difficult.

The literature is contradictory with respect to the prognostic relevance of 9p abnormalities/*CDKN2A* deletions in childhood ALL.[20, 35-40] The evidence from paediatric T-ALL cohorts is more consistent for a relationship between *CDKN2A*/9p deletions and an inferior outcome.[41, 42] However, it should be noted that not all patients with an abnormality of 9p have a *CDKN2A* deletion and vice versa.[1, 35, 43] Therefore the terms are not mutually exclusive, despite considerable overlap. Our cytogenetic based observations are consistent with the recent EORTC study on paediatric BCP-ALL, which used molecular methods to assess *CDKN2A* copy number, and found no evidence for an association between *CDKN2A* deletion and outcome.[38]

Numerous studies over the past five years have shown that outcome after relapse is highly heterogenous.[3] While there is a consensus regarding the most relevant risk factors governing post-relapse survival (initial response, time of relapse and site of relapse) less is known about the relationship between cytogenetics and these factors. Using a cytogenetic risk index outlined in Table 3, we found a strong correlation between poor risk cytogenetics and slow early response as well as early relapse. Furthermore there was a strong correlation between cytogenetic risk group and the relapse risk groups used in UKALLR2.[13] These findings could be used in conjunction with MRD data to identify patients at greatest risk of multiple treatment failure who would benefit most from early intervention with alternative therapies.

This study has many strengths including size, long follow-up, quality and extent of cytogenetic analysis and comprehensive statistical analysis. However, it does have some limitations. As this is the first time that the cytogenetic risk groups in table 4 have been proposed in childhood ALL, they will require validation in independent cohorts. Recent array studies have highlighted a plethora of novel focal deletions of B-cell differentiation and cell cycle genes in childhood ALL.[32, 44] Unfortunately we have not been able to incorporate data on these abnormalities into this study due to a lack of suitable material. Although, *IKZF1* deletions have been reported to confer a higher risk of relapse, the largest effect was seen within the t(9;22) subgroup which is already a well established poor risk subgroup.[44] In addition, den Boer et al[32] reported that many of the micro-deletions correlated with either the t(9;22)/*BCR-ABL1* subgroup or the newly described *BCR-ABL1*-like subgroup. Importantly, the *BCR-ABL1*-like subgroup did not correlate with any of the major cytogenetic subgroups. Hence while it will be important to assess the prognostic relevance of these micro-deletions in the context of these results; we do not think that the absence of such data significantly alters the key findings in this study.

The findings from this large and comprehensively characterised cohort of childhood ALL demonstrate the importance of cytogenetics in the management of patients with this disease. We have confirmed that individual chromosomal abnormalities are strong independent predictors of outcome, especially risk of relapse. Moreover, we have shown that diagnostic cytogenetics not only identifies patients with a higher rate of relapse but predicts those who are less likely to respond well to treatment after relapse. In the forthcoming NCRI ALL2010 paediatric trial the following chromosomal abnormalities will be classified as high risk - t(9;22), iAMP21, *MLL* translocations, near haploidy, low hypodiploidy and t(17;19).

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Critical appraisal and final approval of manuscript: All authors

Conflicts of interests

None of the authors have any conflicts of interest to disclose.

Figure Legends

Figure 1: ALL97/99 treatment regimens.
CMT=Continuing maintenance therapy. MTX=Methotrexate. WCC=white blood cell count. RER=rapid early response. SER=slow early response. CCG=Children's Cancer Study Group. BFM=Berlin Frankfurt Munster consolidation. DDI=double delayed intensification. IM=interim maintenance. DI=delayed intensification. CT=continuing therapy. * Third block was randomised in first year.

Figure 2: Kaplan Meier graphs showing the relapse free survival for (a) individual chromosomal abnormalities that were significant in univariate analysis, (b) cytogenetic risk groups.
For the purposes of drawing this graph patients were classified hierarchically in the order *ETV6-RUNX1*, t(9;22), *MLL* translocations, iAMP21, high hyperdiploidy, abnormal 17p, loss of 13q.

References

1 Harrison CJ, Johannson B. Acute Lymphoblastic Leukaemia. In: Heim S, Mitelman F, eds. *Cancer Cytogenetics*. Third Edition ed. New Jersey: Wiley-Blackwell 2009:233-96.

2 Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006;354(2):166-78.

3 Bailey LC, Lange BJ, Rheingold SR, Bunin NJ. Bone-marrow relapse in paediatric acute lymphoblastic leukaemia. The lancet oncology. 2008 Sep;9(9):873-83.

4 Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TO. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. British Journal of Haematology. 2005;129(6):734-45.

5 Mitchell C, Payne J, Wade R, Vora A, Kinsey S, Richards S, et al. The impact of risk stratification by early bone-marrow response in childhood lymphoblastic leukaemia: results from the United Kingdom Medical Research Council trial ALL97 and ALL97/99. Br J Haematol. 2009 Aug;146(4):424-36.

6 Vora A, Mitchell CD, Lennard L, Eden TO, Kinsey SE, Lilleyman J, et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. Lancet. 2006;368(9544):1339-48.

7 UK National External Quality Assessment Scheme (NEQAS) For Clinical Cytogenetics. 2010 [cited; Available from: http://www.ccneqas.org.uk/

8 Harrison CJ, Martineau M, Secker-Walker LM. The Leukaemia Research Fund / United Kingdom Cancer Cytogenetics Group karyotype database in acute lymphoblastic leukaemia: A valuable resource for patient management. British Journal of Haematology. 2001;113(1):3-10.

9 An International System for Human Cytogenetic Nomenclature. Basel, Switzerland: S. Karger 2005.

10 Harrison CJ, Moorman AV, Barber KE, Broadfield ZJ, Cheung KL, Harris RL, et al. Interphase molecular cytogenetic screening for chromosomal abnormalities of prognostic significance in childhood acute lymphoblastic leukaemia: a UK Cancer Cytogenetics Group Study. British Journal of Haematology. 2005;129(4):520-30.

11 Sutcliffe MJ, Shuster JJ, Sather HN, Camitta BM, Pullen J, Schultz KR, et al. High concordance from independent studies by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favorable prognosis with combined trisomies 4, 10, and 17 in children with NCI Standard-Risk B-precursor Acute Lymphoblastic Leukemia: a Children's Oncology Group (COG) initiative. Leukemia. 2005 May;19(5):734-40.

12 Moorman AV, Richards SM, Martineau M, Cheung KL, Robinson HM, Jalali GR, et al. Outcome heterogeneity in childhood high-hyperdiploid acute lymphoblastic leukemia. Blood. 2003;102(8):2756-62.

13 Roy A, Cargill A, Love S, Moorman AV, Stoneham S, Lim A, et al. Outcome after first relapse in childhood acute lymphoblastic leukaemia - lessons from the United Kingdom R2 trial. BrJHaematol. 2005;130(1):67-75.

14 Shurtleff SA, Buijs A, Behm FG, Rubnitz JE, Raimondi SC, Hancock ML, et al. TEL/AML1 fusion resulting from a cryptic t(12;21) is the most common genetic lesion in pediatric ALL and defines a subgroup of patients with an excellent prognosis. Leukemia. 1995;9:1985-9.

15 Rubnitz JE, Wichlan D, Devidas M, Shuster J, Linda SB, Kurtzberg J, et al. Prospective analysis of TEL gene rearrangements in childhood acute lymphoblastic leukemia: a Children's Oncology Group study. J Clin Oncol. 2008 May 1;26(13):2186-91.

16 Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009 Jun 25;360(26):2730-41.

17 Forestier E, Heyman M, Andersen MK, Autio K, Blennow E, Borgstrom G, et al. Outcome of ETV6/RUNX1-positive childhood acute lymphoblastic leukaemia in the NOPHO-ALL-1992 protocol: frequent late relapses but good overall survival. Br J Haematol. 2008 Mar;140(6):665-72.
18 Seeger K, Buchwald D, Peter A, Taube T, von Stackelberg A, Schmitt G, et al. TEL-AML1 fusion in relapsed childhood acute lymphoblastic leukemia. Blood. 1999;94(1):374-6.
19 Tsang KS, Li CK, Chik KW, Shing MM, Tsoi WC, Ng MH, et al. TEL/AML1 rearrangement and the prognostic significance in childhood acute lymphoblastic leukemia in Hong Kong. American Journal of Hematology. 2001;68(2):91-8.
20 Hann I, Vora A, Harrison G, Harrison C, Martineau M, Moorman AV, et al. Determinants of outcome after intensified therapy of childhood lymphoblastic leukaemia: results from Medical Research Council United Kingdom acute lymphoblastic leukaemia XI protocol. British Journal of Haematology. 2001;113(1):103-14.
21 Pui CH, Chessells JM, Camitta B, Baruchel A, Biondi A, Boyett JM, et al. Clinical heterogeneity in childhood acute lymphoblastic leukemia with 11q23 rearrangements. Leukemia. 2003;17(4):700-6.
22 Pui CH, Gaynon PS, Boyett JM, Chessells JM, Baruchel A, Kamps W, et al. Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. Lancet. 2002;359:1909-15.
23 Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, et al. Outcome of infants less than one year of age with acute lymphoblastic leukemia treated with the Interfant-99 protocol. Lancet. 2007;in press.
24 Stam RW, Schneider P, Hagelstein JA, van der Linden MH, Stumpel DJ, de Menezes RX, et al. Gene expression profiling-based dissection of MLL translocated and MLL germline acute lymphoblastic leukemia in infants. Blood. 2009 Dec 23.
25 Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, et al. Refinement of cytogenetic classification in acute myeloid leukemia: Determination of prognostic significance of rare recurring chromosomal abnormalities amongst 5,876 younger adult patients treated in the UK Medical Research Council trials. Blood. 2009;Submitted.
26 Marks DI, Paietta EM, Moorman AV, Richards SM, Buck G, Dewald G, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics and outcome from the large randomised prospective trial (UKALL XII/ECOG 2993). Blood. 2009;114(25):5136-45.
27 Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): Analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII / Eastern Cooperative Oncology Group (ECOG) 2993 Trial. Blood. 2007;109(8):3189-97.
28 Schoch C, Kern W, Kohlmann A, Hiddemann W, Schnittger S, Haferlach T. Acute myeloid leukemia with a complex aberrant karyotype is a distinct biological entity characterized by genomic imbalances and a specific gene expression profile. Genes, chromosomes & cancer. 2005 Jul;43(3):227-38.
29 Marks DI, Kurz BW, Link MP, Ng E, Shuster JJ, Lauer SJ, et al. High incidence of potential p53 inactivation in poor outcome childhood acute lymphoblastic leukemia at diagnosis. Blood. 1996 Feb 1;87(3):1155-61.
30 Heerema NA, Sather HN, Sensel MG, Lee MK, Hutchinson RJ, Nachman JB, et al. Abnormalities of chromosome bands 13q12 to 13q14 in childhood acute lymphoblastic leukemia. J Clin Oncol. 2000 Nov 15;18(22):3837-44.
31 Jeha S, Pei D, Raimondi SC, Onciu M, Campana D, Cheng C, et al. Increased risk for CNS relapse in pre-B cell leukemia with the t(1;19)/TCF3-PBX1. Leukemia. 2009 Aug;23(8):1406-9.

32 Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. The lancet oncology. 2009 Feb;10(2):125-34.
33 Forestier E, Gauffin F, Andersen MK, Autio K, Borgstrom G, Golovleva I, et al. Clinical and cytogenetic features of pediatric dic(9;20)(p13.2;q11.2)-positive B-cell precursor acute lymphoblastic leukemias: a Nordic series of 24 cases and review of the literature. Genes, chromosomes & cancer. 2008 Feb;47(2):149-58.
34 An Q, Wright SL, Moorman AV, Parker H, Griffiths M, Ross FM, et al. Heterogeneous breakpoints in patients with acute lymphoblastic leukemia and the dic(9;20)(p11-13;q11) show recurrent involvement of genes at 20q11.21. Haematologica. 2009 Aug;94(8):1164-9.
35 Heerema NA, Sather HN, Sensel MG, Liu-Mares W, Lange BJ, Bostrom BC, et al. Association of Chromosome Arm 9p Abnormalities With Adverse Risk in Childhood Acute Lymphoblastic Leukemia: A Report From the Children's Cancer Group. Blood. 1999;94(5):1537-44.
36 Carter TL, Watt PM, Kumar R, Burton PR, Reaman GH, Sather HN, et al. Hemizygous p16(INK4A) deletion in pediatric acute lymphoblastic leukemia predicts independent risk of relapse. Blood. 2001;97(2):572-4.
37 Dalle JH, Fournier M, Nelken B, Mazingue F, Lai JL, Bauters F, et al. p16INK4a immunocytochemical analysis is an independent prognostic factor in childhood acute lymphoblastic leukemia. Blood. 2002;99(7):2620-3.
38 Mirebeau D, Acquaviva C, Suciu S, Bertin R, Dastugue N, Robert A, et al. The prognostic significance of CDKN2A, CDKN2B and MTAP inactivation in B-lineage acute lymphoblastic leukemia of childhood. Results of the EORTC studies 58881 and 58951. Haematologica. 2006;91(7):881-5.
39 van Zutven LJ, van Drunen E, de Bont JM, Wattel MM, den Boer ML, Pieters R, et al. CDKN2 deletions have no prognostic value in childhood precursor-B acute lymphoblastic leukaemia. Leukemia. 2005;19(7):1281-4.
40 Graf Einsiedel H, Taube T, Hartmann R, Wellmann S, Seifert G, Henze G, et al. Deletion analysis of p16INKa and p15INKb in relapsed childhood acute lymphoblastic leukemia. Blood. 2002;99(12):4629-31.
41 Fizzotti M, Cimino G, Pisegna S, Alimena G, Quartarone C, Mandelli F, et al. Detection of homozygous deletions of the cyclin-dependent kinase 4 inhibitor (p16) gene in acute lymphoblastic leukemia and association with adverse prognostic features. Blood. 1995 May 15;85(10):2685-90.
42 Diccianni MB, Batova A, Yu J, Vu T, Pullen J, Amylon M, et al. Shortened survival after relapse in T-cell acute lymphoblastic leukemia patients with p16/p15 deletions. Leuk Res. 1997 Jun;21(6):549-58.
43 Sulong S, Moorman AV, Irving JA, Strefford JC, Konn ZJ, Case MC, et al. A comprehensive analysis of the CDKN2A gene in childhood acute lymphoblastic leukaemia reveals genomic deletion, copy number neutral loss of heterozygosity and association with specific cytogenetic subgroups. Blood. 2009 Oct 6;113(1):100.
44 Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al. Deletion of IKZF1 and Prognosis in Acute Lymphoblastic Leukemia. N Engl J Med. 2009 Jan 7;360(5):470-80.

Tables

Table 1: Outcome of children with B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) by chromosomal abnormality and cytogenetic risk group

Chromosomal abnormality	Total (%)	No remission No. (%)	No.(%) of deaths in 1st remission	No.(%) of relapse	Relapse Free Survival		Event Free Survival		Overall Survival	
					at 5 yrs (95%CI)	Hazard Ratio (95% CI)[1]	at 5 yrs (95%CI)	Hazard Ratio (95% CI)	at 5 yrs (95%CI)	Hazard Ratio (95% CI)
All patients	1725(100%)	16 (1%)	57 (3%)	351 (20%)	81% (79-83%)	-	78% (76-80%)		87% (86-89%)	-
Primary abnormalities										
High hyperdiploidy	562 (38%)	3 (1%)	11 (2%)	85 (15%)	86% (83-89%)	0.60 (0.47,0.78)***	84% (81-87%)	0.58(0.46,0.74)***	93% (91-95%)	0.45(0.33-0.63)***
ETV6-RUNX1	368 (25%)	2 (1%)	5 (1%)	47 (13%)	89% (86-92%)	0.51 (0.38,0.70)***	89% (85-91%)	0.48(0.36,0.65)***	96% (94-98%)	0.29(0.18-0.47)***
t(1;19)(q23;p13)	50 (4%)	0 (0%)	4 (8%)	6 (12%)	87% (74-94%)	0.60 (0.27,1.35)	80% (66-89%)	0.85(0.45,1.59)	84% (71-92%)	1.29(0.66,2.52)
t(9;22)(q34;q11.2)	43 (3%)	1 (2%)	7 (16%)	18 (42%)	56% (38-70%)	3.55 (2.21,5.72)***	44% (29-58%)	4.10(2.75,6.11)***	58% (42-71%)	4.48(2.80,7.16)***
iAMP21	29 (2%)	1 (3%)	0 (0%)	22 (76%)	27% (12-44%)	6.04 (3.90,9.35)***	26% (12-43%)	4.91(3.21,7.5)***	69% (49-82%)	3.57(2.00,6.40)***
MLL translocations	30 (2%)	0 (0%)	2 (7%)	13 (43%)	55% (35-71%)	2.98 (1.71,5.20)**	50% (31-66%)	2.79(1.66,4.67)***	60% (41-75%)	3.34(1.87,5.98)***
Near Haploidy	10 (1%)	0 (0%)	0 (0%)	6 (60%)	44% (14-72%)	-	40% (12-67%)	-	40% (12-67%)	-
Low hypodiploidy	8 (1%)	0 (0%)	0 (0%)	4 (50%)	50% (15-78%)	-	50% (15-78%)	-	50% (15-78%)	-
IGH-CEBP	7 (NA)	0 (0%)	0 (0%)	2 (29%)	71% (26-92%)	-	71% (26-92%)	-	86% (33-98%)	-
IGH-ID4	3 (NA)	0 (0%)	0 (0%)	0 (0%)	100%	-	100%	-	100%	-
t(17;19)(q23;p13)	2 (0.1%)	0 (0%)	0 (0%)	2 (100%)	-	-	-	-	-	-
Secondary abnormalities										
del(6q)	77 (5%)	0 (0%)	2 (3%)	17 (22%)	80% (69-87%)	1.09 (0.67,1.78)	79% (68-87%)	1.02(0.64,1.62)	87% (77-93%)	1.08(0.61,1.94)
abnormal 9p	160 (11%)	2 (1%)	5 (3%)	38 (24%)	77% (70-83%)	1.32 (0.93,1.85)	74% (67-80%)	1.28(0.94,1.75)	86% (79-90%)	1.06(0.69,1.63)
abnormal 11q	68 (5%)	1 (2%)	3 (4%)	12 (18%)	81% (70-89%)	0.89 (0.50,1.58)	78% (66-86%)	0.93(0.56,1.56)	87% (76-93%)	1.14(0.62,2.10)
abnormal 17p	50 (4%)	1 (2%)	0 (0%)	18 (36%)	65% (50-77%)	2.09 (1.30,3.37)*	64% (49-76%)	1.81(1.14,2.88)	76% (61-86%)	1.96(1.12,3.44)
Loss of 13q	44 (3%)	2 (5%)	1 (2%)	14 (32%)	68% (52-80%)	1.87 (1.09,3.20)	66% (50-78%)	1.88(1.15,3.06)	82% (67-91%)	1.35(0.67,2.73)
dup(1q)	41 (3%)	1 (2%)	0 (0%)	8 (20%)	82% (66-91%)	0.93 (0.46,1.88)	80% (64-90%)	0.88(0.46,1.71)	95% (82-99%)	0.48(0.15,1.50)
-7	23 (2%)	1 (4%)	0 (0%)	7 (30%)	77% (54-90%)	1.61 (0.76,3.40)	74% (51-87%)	1.53(0.76,3.08)	87% (65-96%)	0.92(0.30,2.88)
dic(9;20)(p13;q11)	13 (1%)	0 (0%)	1 (8%)	3 (23%)	77% (44-92%)	1.13 (0.36,3.53)	77% (44-92%)	1.26(0.47,3.38)	92% (57-99%)	1.02(0.25,4.10)
dic(9;12)(p11~21;p11~13)	15 (1%)	0 (0%)	0 (0%)	3 (20%)	80% (50-93%)	1.04(0.33,3.24)	80% (50-93%)	0.87(0.28,2.7)	87% (56-97%)	0.95(0.24,3.81)
Cytogenetic Risk Group [1]										
Good Risk	923	5 (1%)	15 (2%)	129 (14%)	88% (85-90%)	0.59 (0.45,0.77)***	86% (84-88%)	0.55(0.43,0.69)***	94% (93-96%)	0.37(0.27,0.52)***
Intermediate Risk	458	5 (1%)	23 (5%)	98 (21%)	80% (76-84%)	1	76% (72-80%)	1	85% (81-88%)	1
Poor Risk	166	4 (2%)	10 (6%)	82 (49%)	50% (42-58%)	3.19 (2.38,4.29)***	45% (37-52%)	2.91(2.23,3.80)***	61% (53-68%)	2.82(2.04,3.88)***

Notes: (1) Hazard ratio is from a univariate Cox regression model comparing the relapse risk of patient with and without the chromosomal abnormality under consideration. For the good and poor cytogenetic risk groups each has been compared to the intermediate group. (2) See table 4 for definition of cytogenetic risk group. **Abbreviations:** CI, confidence interval; **Symbols:** * *P* <0.01; ** *P* <0.001; ***P<0.0001; **Definitions:** High hyperdiploidy, 51-65 chromosomes; near haploidy, <30 chromosomes; low hypodiploidy, 30-39 chromosomes.

Table 2: Final multivariate Cox models of relapse free survival for individual chromosomal abnormalities and the cytogenetic risk groups

Variable [1]	Hazard Ratio [3]	*P* value	95% CI
Individual chromosomal abnormality [6]			
ALL99 v ALL97	0.71	0.0031	(0.56,0.89)
Dexa v Pred [4]	0.62	0.0001	(0.49,0.79)
iAMP21	4.69	<0.0001	(2.94,7.48)
WCC [2]	1.23	<0.0001	(1.13,1.35)
Age	1.05	0.0003	(1.02,1.08)
t(9;22)	2.65	0.0001	(1.62,4.35)
ETV6-RUNX1	0.53	0.0002	(0.38,0.74)
High hyperdiploidy	0.68	0.0065	(0.51,0.90)
Abnormal 17p	2.21	0.0012	(1.37,3.57)
Loss of 13q	1.99	0.0130	(1.16,3.43)
Cytogenetic Risk Group [5]			
ALL99 v ALL97	0.70	0.0019	(0.55,0.87)
Dexa v Pred [4]	0.62	0.0001	(0.49,0.79)
Good v Intermediate Risk	0.70	0.0110	(0.53,0.92)
Poor v Intermediate Risk	3.01	<0.0001	(2.23,4.06)
WCC [2]	1.16	0.0010	(1.06,1.26)
Age	1.05	0.0004	(1.02,1.08)

Notes: (1) Variables are listed in the order in which they entered the model; (2) WCC was transformed to ln(WCC+1) before being entered in the model; (3) The hazard ratio for the good and poor cytogenetic risk groups is relative to the intermediate risk group; (4) Dexamethasone v Prednisolone; (5) See table 4 for definition of cytogenetic risk group; (6) Sex and *MLL* translocations were assessed in the stepwise multivariate analysis but did not make it into the final model.

Abbreviations: WCC, white cell count

Definitions: High hyperdiploidy, 51-65 chromosomes

Table 3: Definition of cytogenetic risk groups

Cytogenetic Risk Group	Chromosomal abnormalities	Notes
Good	High hyperdiploidy (51-65 chromosomes) *ETV6-RUNX1*	Irrespective of the presence of poor risk abnormalities, except t(9;22)(q34;q11).
Intermediate	t(1;19)(q23;p13) *IGH-CEBP* *IGH-ID4* del(6q) abnormal 9p abnormal 11q dup(1q) -7 dic(9;20)(p13;q11) dic(9;12)(p11~21;p11~13) any other abnormality normal karyotype	
Poor	t(9;22)(q34;q11.2) iAMP21 *MLL* translocations near Haploidy (<30 chromosomes) low hypodiploidy (30-39 chromosomes) t(17;19)(q23;p13) abnormal 17p loss of 13q	In the absence of good risk abnormalities, except in the situation of t(9;22) with high hyperdiploidy.

Table 4: Relationship between cytogenetic risk group and response rate, time of relapse, site of relapse and relapse risk group.

Relapse Criteria	All cases [1] n (%)	Cytogenetic Risk Group n (%) [2]		
		Good	Intermediate	Poor
Total Relapses	309 (20%)	129 (100%)	98 (100%)	82 (100%)
Time of relapse				
<18m	69 (22%)	8 (6%)	24 (25%)	37 (45%)
>18m and <6m EOT	67 (22%)	28 (22%)	25 (26%)	14 (17%)
>6m EOT	173 (56%)	93 (72%)	49 (50%)	31 (38%)
Site of relapse				
Isolated marrow	180 (58%)	69 (54%)	57 (58%)	54 (66%)
Isolated CNS	51 (17%)	22 (17%)	19 (19%)	10 (12%)
Isolated other	15 (5%)	8 (6%)	4 (4%)	3 (4%)
Combined	63 (20%)	30 (23%)	18 (18%)	15 (18%)
Relapse Risk Group [3]				
Standard Risk	19 (6%)	13 (10%)	3 (3%)	3 (4%)
Intermediate Risk	217 (70%)	104 (81%)	72 (74%)	41 (50%)
High Risk	73 (24%)	12 (9%)	23 (24%)	38 (46%)

Notes:

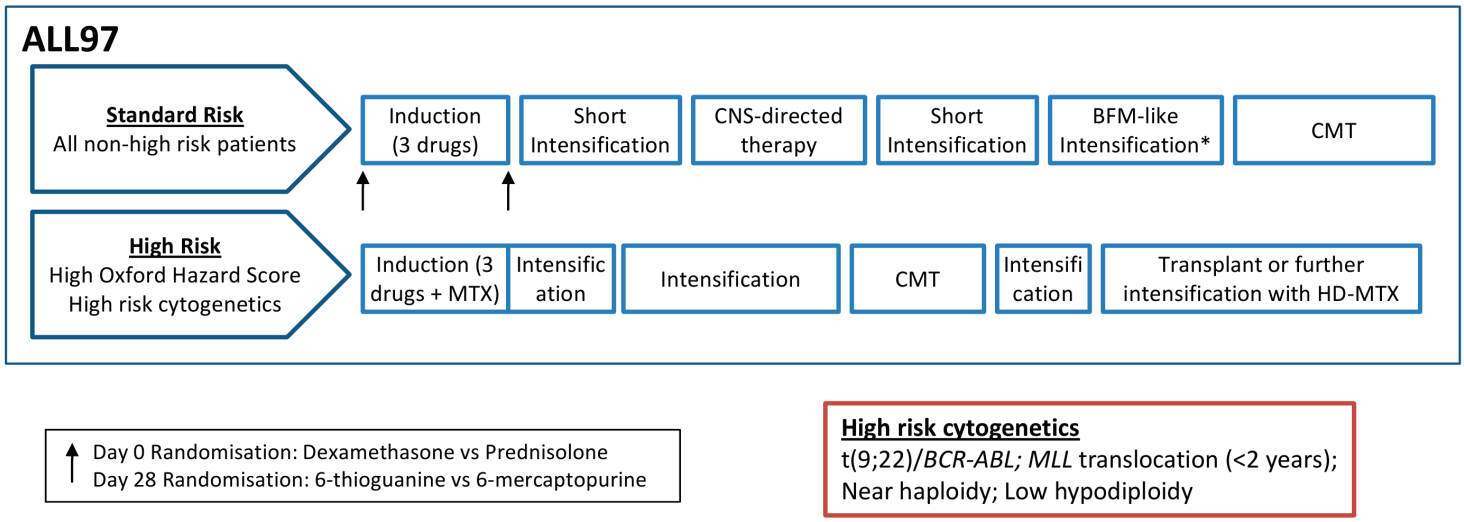
(1) Excludes cases with failed or no cytogenetics.

(2) See table 4 for definition of cytogenetic risk group

(3) Standard risk, isolated extramedullary relapses occurring 6 months or more after the EOT; Intermediate risk, isolated extramedullary relapses occurring on therapy or within 6 months of EOT, combined relapses occurring 18m or more after diagnosis and isolated marrow relapses occurring 6 months after the EOT; High risk, combined relapses occurring with 18m of diagnosis and isolated marrow relapses occurring on therapy or within 6 months of EOT.

Abbreviations: EOT, end of frontline treatment

Figure 1



↑ Day 0 Randomisation: Dexamethasone vs Prednisolone
Day 28 Randomisation: 6-thioguanine vs 6-mercaptopurine

High risk cytogenetics
t(9;22)/*BCR-ABL; MLL* translocation (<2 years);
Near haploidy; Low hypodiploidy

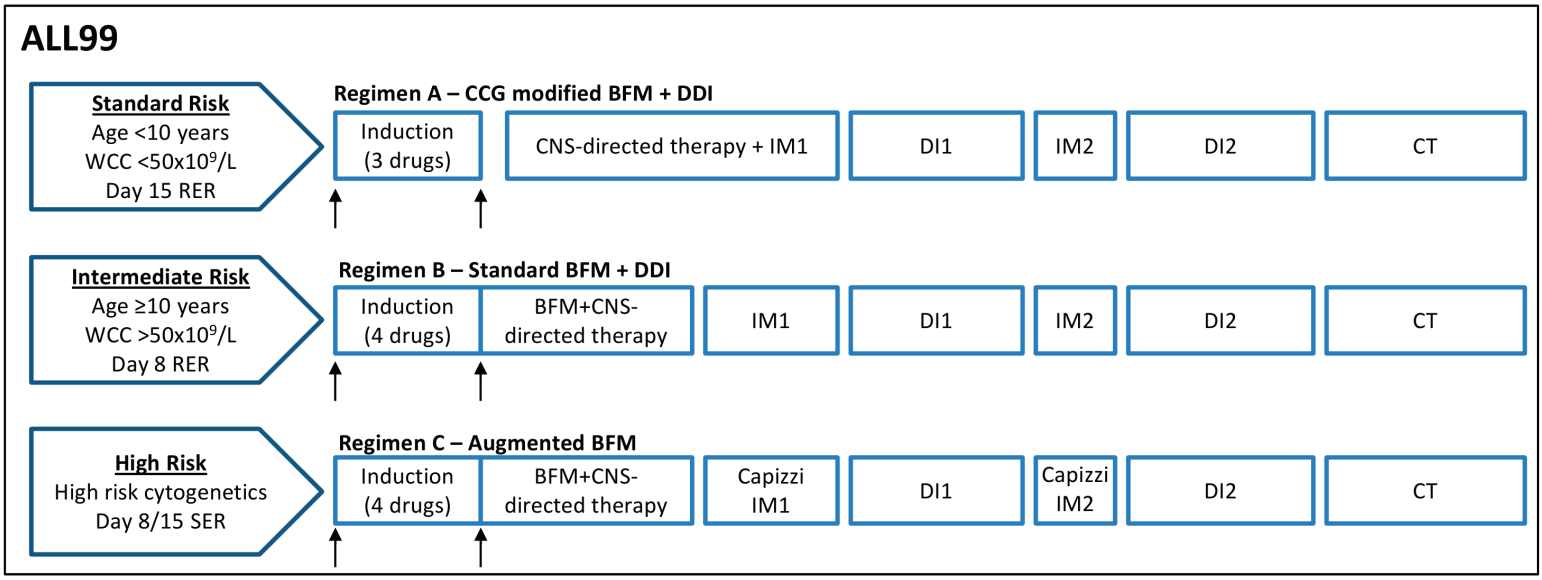
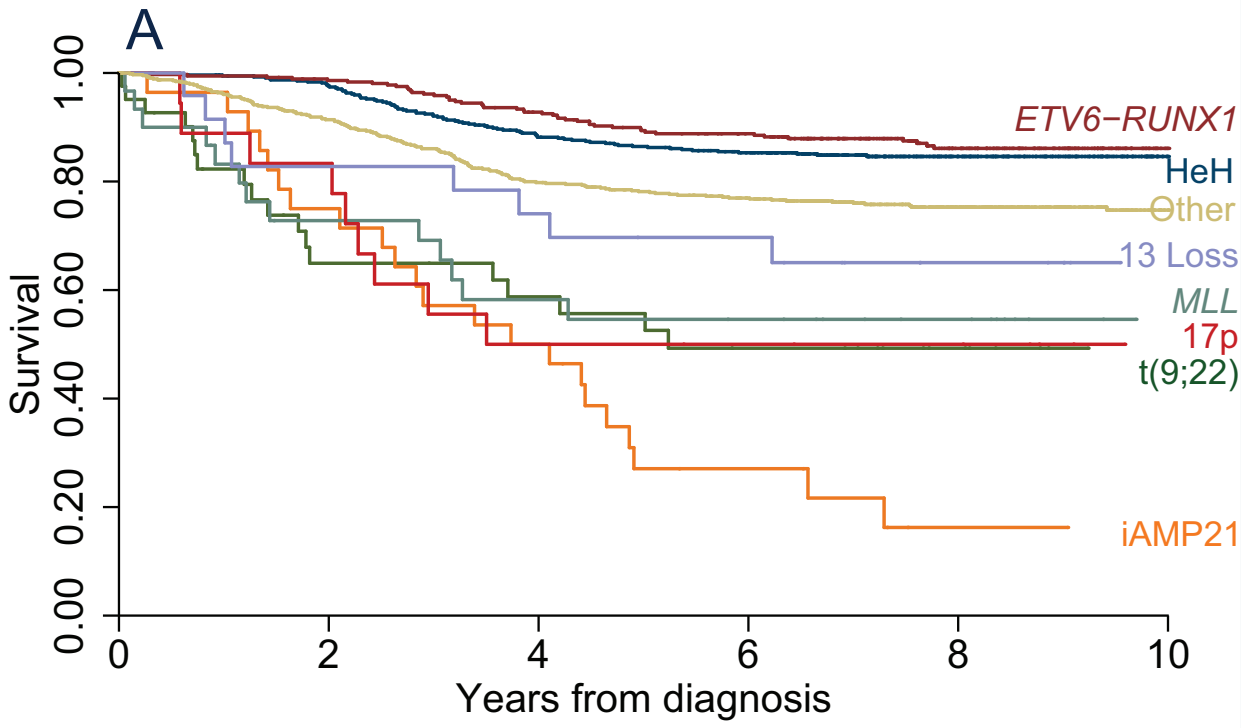


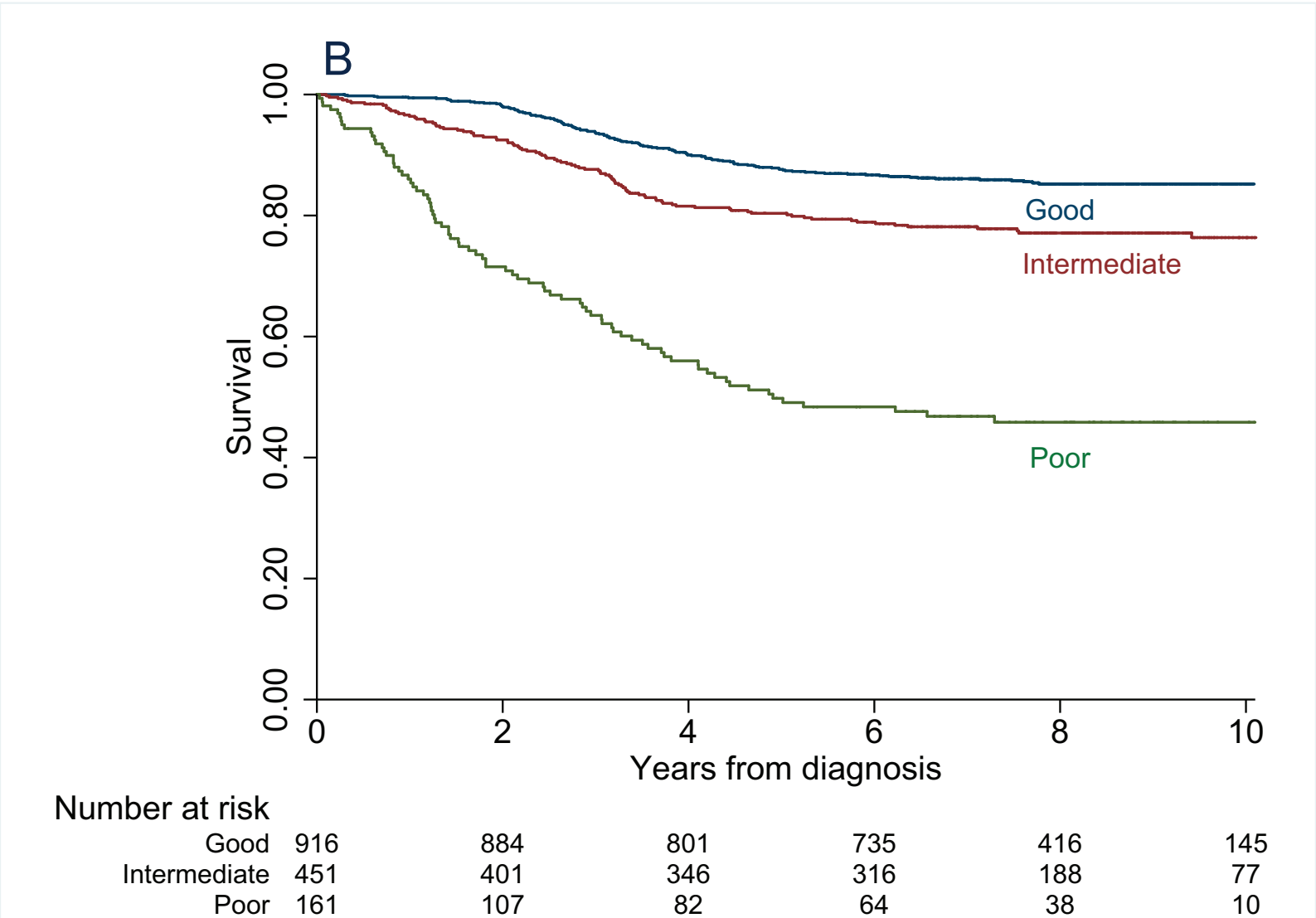
Figure 2a



Number at risk

(HeH) High hyperdiplody	551	529	470	434	249	98
ETV6−RUNX1	365	355	331	301	167	47
t(9;22)(q34;q11)	42	22	19	14	8	2
iAMP21	28	21	14	6	1	0
MLL translocations	30	20	16	14	9	1
Abnormal17p	18	15	9	8	7	2
13q loss	24	19	17	15	9	4
Other	644	567	483	440	258	105

Figure 2b


B
Survival
0.00
0.20
0.40
0.60
0.80
1.00
0
2
4
6
8
10
Years from diagnosis
Good
Intermediate
Poor
Number at risk
Good 916 884 801 735 416 145
Intermediate 451 401 346 316 188 77
Poor 161 107 82 64 38 10

Supplementary Information for Moorman et al (2010) The prognostic impact of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: Results from the MRC ALL97/99 randomised trial. Lancet Oncology, Vol XXX, Page, XXX

Supplementary Table 1: Co-existence of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia (BCP-ALL).

	High hyperdiploid	*ETV6-RUNX1*	t(1;19)	t(9;22)	iAMP21	*MLL* translocations	Haploidy	Low hypo	*IGH-CEBP*	*IGH-ID4*	t(17;19)	del(6q)	abnormal 9p	abnormal 11q	Abnormal 17p	Loss of 13q	dup(1q)	-7	dic(9;20)	dic(9;12)
High hyperdiploid	562	2		5								17	17	10	21	5	38	3		
ETV6-RUNX1	2	368										33	22	32	6	11				5
t(1;19)			50									7	8	1		5				
t(9;22)	5			43									10	1	1	2	1	3		
iAMP21					29								2	3	1	1		1		
MLL translocations						30							2	1	2					
Haploidy							10													
Low hypo								8				1								
IGH-CEBP									7						1					
IGH-ID4										3			3		2					
t(17;19)											2									
del(6q)	17	33	7		1			1				77	9	9	5	4				
abnormal 9p	17	22	8	10	2	2				3		9	160	7	11	10	1	4	13	14
abnormal 11q	10	32	1	1	3	1						9	7	67	1	5	1			1
abnormal 17p	21	6		1	1	2			1	2		5	11	1	50	1	4		1	2
Loss of 13q	5	11	5	2	1							4	10	5	1	44	1	3		1
dup(1q)	38			1									1	1	4	1	41			
-7	3			3	1								4			3		23		
dic(9;20)													13		1				13	
dic(9;12)		5											14	1	2	1				15

Supplementary Table 2: Incidence and clinical characteristics of children with B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) by chromosomal abnormality and cytogenetic risk group

Chromosomal abnormality	Number (%) of patients [1]	Sex ratio (M:F)	Age (years) Median (IQR)	WCC (x10^9/L) Median (IQR)
All patients	1725 (100%)	1:0.83	4 (3,8)	9.9 (4.2,31.5)
Primary Chromosomal/Genetic abnormalities				
High hyperdiploidy	562 (38%)	1: 0.8	3 (2,6)**	7.5 (3.7,19.7)**
ETV6-RUNX1	368 (25%)	1: 0.7	4 (3,5) **	10.7 (5, 33.7)
t(1;19)(q23;p13)	50 (4%)	1:1.27	3 (2,8)	26.2 (16.2, 39)**
t(9;22)(q34;q11.2)	43 (3%)	1:0.65	6 (3,12)	35 (11,200)**
iAMP21	29 (2%)	1:0.93	8 (7,12)**	3.7 (2.4,13.9)**
MLL translocations	30 (2%)	1:0.88	4 (1,12)	129 (32,205)**
Near Haploidy	10 (1%)	1:1	6 (4,8)	50 (16,135)*
Low hypodiploidy	8 (1%)	1:1	12 (10,14)*	5.6 (4.1,14.2)
IGH-CEBP	7 (NA)	1:1.33	11 (9,14)*	5.9 (4.6,103)
IGH-ID4	3 (NA)	1:0	12	4.5
t(17;19)(q23;p13)	2 (0.1%)	1:1	9	6.7
Secondary abnormalities				
del(6q)	77 (5%)	1:0.67	4 (3,7)	8.5 (3.4,23.4)
abnormal 9p	160 (11%)	1:0.86	6 (3,11)*	12.8 (5.2,58)*
abnormal 11q	68 (5%)	1:1.06	4 (3,8)	8.4 (5,22.2)
abnormal 17p	44 (3%)	1:0.92	5 (3,10)*	9.5 (5.7, 36.5)
Loss of 13q	50 (4%)	1:0.76	6 (4,9)	12.2 (4.6,34)
dup(1q)	41 (3%)	1:0.86	4 (3,7)	9 (4.2,23.7)
-7	23 (2%)	1:0.64	4 (3,12)	11.4 (4,49.6)
dic(9;20)(p13;q11)	13 (1%)	1:0.86	7 (5,11)	10.7 (4.2,20.1)
dic(9;12)(p11~21;p11~13)	15 (1%)	1:0.15	11 (3,14)	15 (3.6, 33.9)
Cytogenetic Risk Group [2]				
Good Risk	923	1:0.77	4 (2,6)**	8.5 (4.1, 24)**
Intermediate Risk	458	1:0.89	5 (3,10)	12.6 (4.6,36.9)
Poor Risk	166	1:0.84	7 (4,12)	16.1 (5.2, 91.5)

Notes: (1) The incidence has been calculated using the total number of patients tested for each abnormality by cytogenetics, FISH or RT-PCR: High hyperdiploidy (n=1486); *ETV6-RUNX1* (n=1451); t(1;19), abnormal 11q, dic(9;12) (n=1420); t(17;19), del(6q), abnormal 9p, abnormal 17p, loss of 13q, dup(1q), -7, dic(9;20) (n=1419); t(9;22) (n=1633); iAMP21 (n=1449), Other *MLL* translocations, t(4;11) (n=1627); near haploidy, low hypodiploidy (n=1434). No incidence has been given for *IGH-CEBP* and *IGH-ID4* has both these abnormalities were identified by selected FISH screening. (2) See table 4 for definition of cytogenetic risk group. For the good and poor cytogenetic risk groups each has been compared to the intermediate group. **Abbreviations:** IQR, inter-quartile range; WCC, white cell count. **Symbols:** * P <0.01, **P<0.001. **Definitions:** High hyperdiploidy, 51-65 chromosomes; near haploidy, <30 chromosomes; low hypodiploidy, 30-39 chromosomes.

Supplementary Table 3: Outcome of children with B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) by chromosomal abnormality and cytogenetic risk group showing the comparator group for individual analyses.

Chromosomal abnormality		Total (%)	No Remission N (%)	Deaths in 1st remission N (%)	Relapses N (%)	RFS at 5 Yrs % (95%CI)	EFS at 5Yrs % (95% CI)	OS at 5Yrs % (95% CI)
All patients		1725 (100)	16 (1)	57 (3)	351 (20)	81 (79-83)	78 (76-80)	87 (86-89)
Primary abnormalities								
High hyperdiploidy	Yes	562 (38)	3 (1)	11 (2)	85 (15)	86 (83-89)	84 (81-87)	93 (91-95)
	No	924 (62)	11(1)	38 (4)	212 (23)	78 (76-81)	75 (72-78)	85 (82-87)
ETV6-RUNX1	Yes	368 (25)	2 (1)	5 (1)	47 (13)	89 (86-92)	89 (85-91)	96 (94-98)
	No	1083 (75)	10 (1)	42 (4)	240 (22)	79 (76-81)	75 (73-78)	85 (83-87)
t(1;19)(q23;p13)	Yes	50 (4)	0 (0)	4 (8)	6 (12)	87 (74-94)	80 (66-89)	84 (71-92)
	No	1370 (97)	13(1)	42 (3)	277 (20)	81 (79-83)	79 (76-81)	88 (86-89)
t(9;22)(q34;q11.2)	Yes	43 (3)	1 (2)	7 (16)	18 (42)	56 (38-70)	44 (29-58)	58 (42-71)
	No	1590 (97)	13 (1)	46 (3)	309 (19)	82 (80-84)	79 (77-81)	89 (87-90)
iAMP21	Yes	29 (2)	1 (3)	0 (0)	22 (76)	27 (12-44)	26 (12-43)	69 (49-82)
	No	1420 (98)	11(1)	46 (3)	266 (19)	83 (80-85)	80 (77-82)	88 (87-90)
MLL translocations	Yes	30 (2)	0 (0)	2 (7)	13 (43)	55 (35-71)	50 (31-66)	60 (41-75)
	No	1597 (98)	14 (1)	51 (3)	315 (20)	82 (80-84)	79 (77-81)	88 (86-90)
Near Haploidy	Yes	10 (1)	0 (0)	0 (0)	6 (60)	44 (14-72)	40 (12-67)	40 (12-67)
	No	1425(99)	14(1)	47 (3)	287 (20)	81 (79-83)	78 (76-80)	88 (86-90)
Low hypodiploidy	Yes	8 (1)	0 (0)	0 (0)	4 (50)	50 (15-78)	50 (15-78)	50 (15-78)
	No	1426(99)	14(1)	47 (3)	289 (20)	81 (79-83)	78 (76-80)	88 (86-89)
IGH-CEBP	Yes	7 (NA)	0 (0)	0 (0)	2 (29)	71 (26-92)	71 (26-92)	86 (33-98)
	No	86 (NA)	3 (4)	7 (8)	28 (33)	70 (59-79)	63 (52-72)	75 (65-83)
IGH-ID4	Yes	3 (NA)	0 (0)	0 (0)	0 (0)	100 (-)	100 (-)	100 (-)
	No	90 (NA)	3 (3)	7(8)	30 (33)	69 (58-78)	62 (51-71)	75 (65-83)
t(17;19)(q23;p13)	Yes	2 (0.1)	0 (0)	0 (0)	2 (100)	-	-	-
	No	1417(99.9)	13(1)	46(3)	281 (20)	82 (80-84)	79 (76-81)	88 (86-89)
Secondary abnormalities								
del(6q)	Yes	77 (5)	0 (0)	2 (3)	17 (22)	80 (69-87)	79 (68-87)	87 (77-93)
	No	1342 (95)	13 (1)	44 (3)	266 (20)	82 (80-84)	79 (76-81)	88 (86-89)
abnormal 9p	Yes	160 (11)	2 (1)	5 (3)	38 (24)	77 (70-83)	74 (67-80)	86 (79-90)
	No	1259 (89)	11 (1)	41 (3)	245 (20)	82 (80-84)	79 (77-81)	88 (86-90)
abnormal 11q	Yes	68 (5)	1 (2)	3 (4)	12 (18)	81 (70-89)	78 (66-86)	87 (76-93)
	No	1352 (95)	12 (1)	43 (3)	271 (20)	82 (79-84)	79 (76-81)	88 (86-89)
abnormal 17p	Yes	50 (4)	1 (2)	0 (0)	18 (36)	65 (50-77)	64 (49-76)	76 (61-86)
	No	1369 (97)	12 (1)	46 (3)	265 (19)	82 (80-84)	79 (77-81)	88 (86-90)
loss of 13q	Yes	44 (3)	2 (5)	1 (2)	14 (32)	68 (52-80)	66 (50-78)	82 (67-91)
	No	1375 (97)	11 (1)	45 (3)	269 (20)	82 (80-84)	79 (77-81)	88 (86-89)
dup(1q)	Yes	41 (3)	1 (2)	0 (0)	8 (20)	82 (66-91)	80 (64-90)	95 (82-99)
	No	1378 (97)	12 (1)	46 (3)	275 (20)	82 (79-84)	79 (76-81)	87 (86-89)
-7	Yes	23 (2)	1 (4)	0 (0)	7 (30)	77 (54-90)	74 (51-87)	87 (65-96)
	No	1396 (98)	12 (1)	46 (3)	276 (20)	82 (80-84)	79 (76-81)	88 (86-89)
dic(9;20)(p13;q11)	Yes	13 (1)	0 (0)	1 (8)	3 (23)	77 (44-92)	77 (44-92)	92 (57-99)
	No	1406 (99)	13 (1)	45 (3)	280 (20)	82 (80-84)	79 (76-81)	88 (86-89)
dic(9;12)(p11~21;p11~3)	Yes	15 (1)	0 (0)	0 (0)	3 (20)	80 (50-93)	80 (50-93)	87 (56-97)
	No	1405 (99)	13 (1)	46 (3)	280 (20)	82 (79-84)	79 (76-81)	88 (86-89)
Cytogenetic Risk Group [1]								
Good Risk	Yes	923 (54)	5 (1)	15 (2)	129 (14)	88 (85-90)	86 (84-88)	94 (93-96)
Intermediate Risk	Yes	458 (27)	5 (1)	23 (5)	98 (21)	80 (76-84)	76 (72-80)	85 (81-88)
Poor Risk	Yes	166 (10)	4 (2)	10 (6)	82 (49)	50 (42-58)	45 (37-52)	61 (53-68)
No Cytogenetic Group	No	178 (10)	2 (1)	9 (5)	42 (24)	77 (69-82)	72 (65-78)	83 (76-87)

Notes: (1) See table 4 for definition of cytogenetic risk group. **Abbreviations:** CI, confidence interval; **Definitions:** High hyperdiploidy, 51-65 chromosomes; near haploidy, <30 chromosomes; low hypodiploidy, 30-39 chromosomes.

Supplementary Table 4: Final multivariate Cox models of Event Free Survival for individual chromosomal abnormalities and the cytogenetic risk groups

Variable [1]	Hazard Ratio [3]	*P* value	95% CI
Individual chromosomal abnormality[6]			
ALL99 v ALL97	0.75	0.0059	(0.60,0.92)
Dexa v Pred [4]	0.71	0.0023	(0.57,0.89)
Age	1.05	0.0001	(1.02,1.08)
WCC [2]	1.23	<0.0001	(1.14,1.34)
iAMP21	3.84	<0.0001	(2.45,6.02)
t(9;22)	2.89	<0.0001	(1.90,4.38)
ETV6-RUNX1	0.49	<0.0001	(0.36,0.68)
High hyperdiploidy	0.65	0.0009	(0.50,0.84)
Abnormal 17p	1.89	0.0072	(1.19,3.01)
Loss of 13q	1.92	0.0097	(1.17,3.13)
Cytogenetic Risk Group [5]			
ALL99 v ALL97	0.74	0.0039	(0.60,0.91)
Dexa v Pred [4]	0.71	0.0023	(0.57,0.89)
Good v Intermediate Risk	0.64	0.0005	(0.50,0.83)
Poor v Intermediate Risk	2.71	<0.0001	(2.07,3.56)
WCC [2]	1.17	0.0001	(1.08,1.26)
Age	1.05	0.0003	(1.02,1.07)

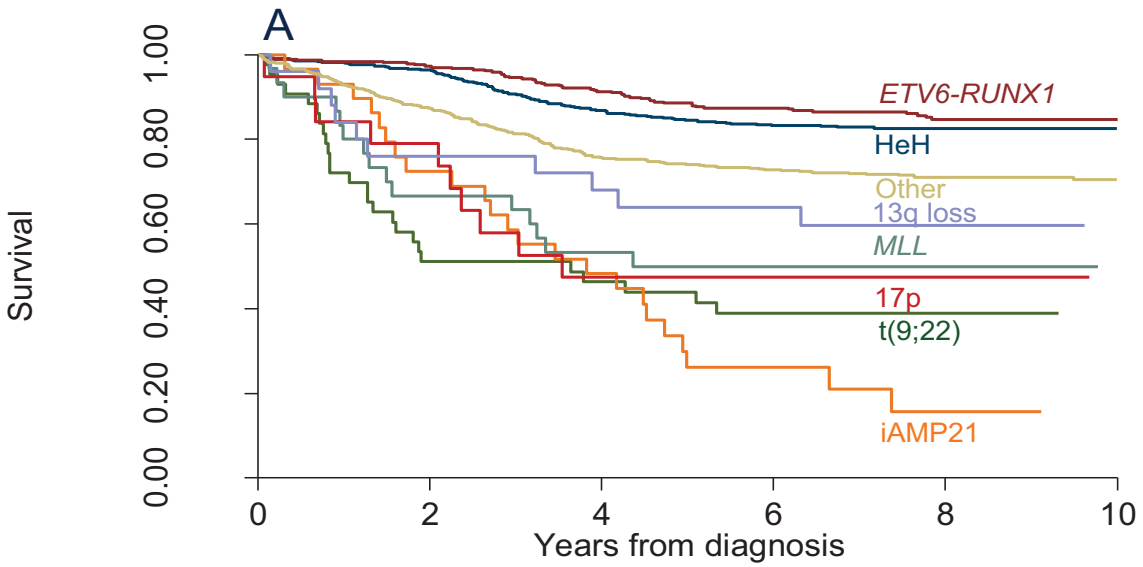
Notes: (1) Variables are listed in the order in which they entered the model; (2) WCC was transformed to ln(WCC+1) before being entered in the model; (3) The hazard ratio for the good and poor cytogenetic risk groups is relative to the intermediate risk group; (4) Dexamethasone v Prednisolone; (5) See table 4 for definition of cytogenetic risk group; (6) Sex and *MLL* translocations were assessed in the stepwise multivariate analysis but did not make it into the final model. **Abbreviations:** WCC, white cell count. **Definitions:** High hyperdiploidy, 51-65 chromosomes

Supplementary Table 5: Final multivariate Cox models of Overall Free Survival for individual chromosomal abnormalities and the cytogenetic risk groups

Variable [1]	Hazard Ratio [3]	*P* value	95% CI
Individual chromosomal abnormality[6]			
ALL99 v ALL97	0.71	0.0150	(0.54,0.94)
Dexa v Pred [4]	0.85	0.2490	(0.64,1.12)
Age	1.07	<0.0001	(1.04,1.11)
WCC [2]	1.33	<0.0001	(1.20,1.47)
ETV6-RUNX1	0.28	<0.0001	(0.17,0.46)
High hyperdiploidy	0.49	0.0001	(0.34,0.69)
t(9;22)	2.42	0.0004	(1.48,3.94)
iAMP21	2.49	0.0033	(1.36,4.59)
Abnormal 17p	1.99	0.0170	(1.13,3.50)
Cytogenetic Risk Group [5]			
ALL99 v ALL97	0.68	0.0069	(0.52,0.90)
Dexa v Pred [4]	0.85	0.2490	(0.64,1.12)
Good v Intermediate Risk	0.48	<0.0001	(0.34,0.67)
Poor v Intermediate Risk	2.50	<0.0001	(1.80,3.48)
WCC [2]	1.27	<0.0001	(1.15,1.40)
Age	1.07	<0.0001	(1.04,1.10)

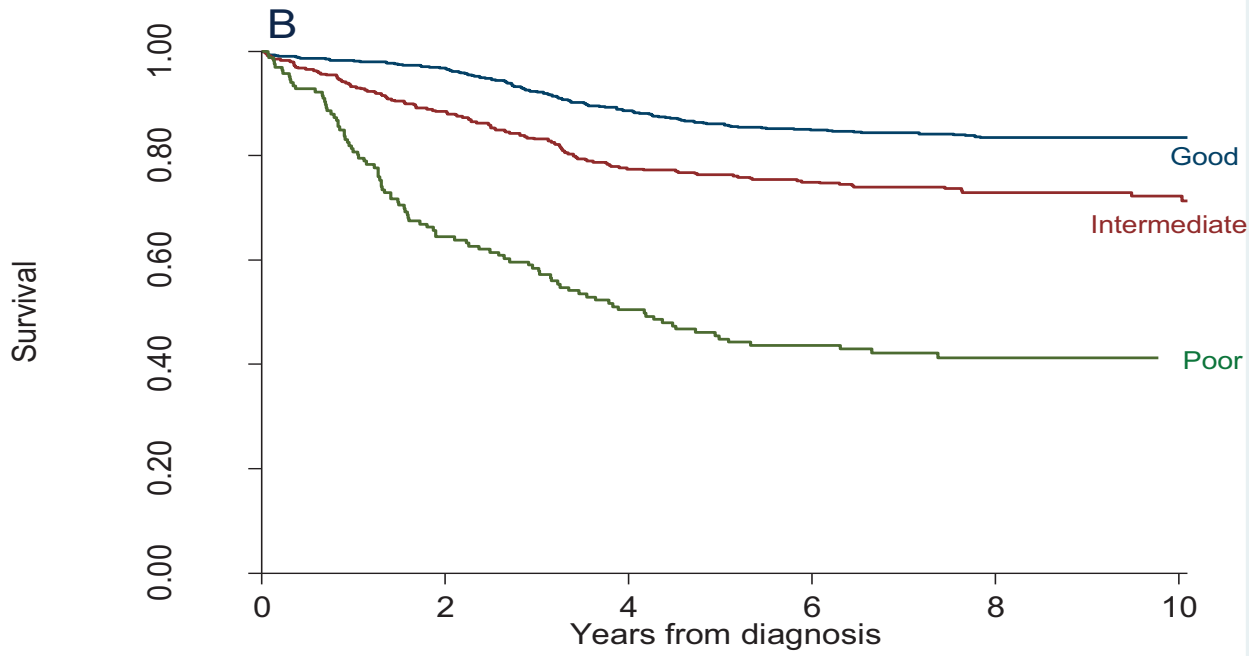
Notes: (1) Variables are listed in the order in which they entered the model; (2) WCC was transformed to ln(WCC+1) before being entered in the model; (3) The hazard ratio for the good and poor cytogenetic risk groups is relative to the intermediate risk group; (4) Dexamethasone Vs Prednisolone; (5) See table 4 for definition of cytogenetic risk group; (6) Sex, *MLL* translocations and loss of 13q were assessed in the stepwise multivariate analysis but did not make it into the final model. **Abbreviations:** WCC, white cell count
Definitions: High hyperdiploidy, 51-65 chromosomes

Supplementary figure 1: Kaplan Meier graphs showing the event free survival for (a) individual chromosomal abnormalities that were significant in univariate analysis, (b) cytogenetic risk groups. NB. For the purposes of drawing this graph patients were classified hierarchically in the order *ETV6-RUNX1*, t(9;22), *MLL* translocations, iAMP21, high hyperdiploidy, abnormal 17p, loss of 13q.



Number at risk

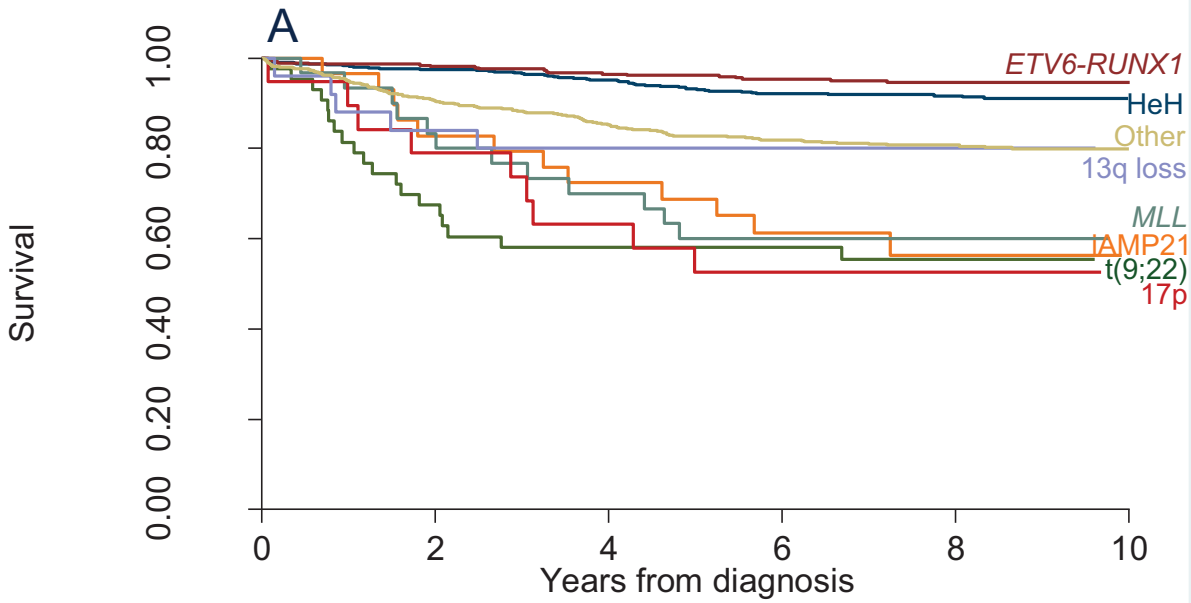
(HeH) High hyperdiplody	555	534	475	437	255	102
ETV6-RUNX1	368	357	332	303	169	51
t(9;22)(q34;q11)	43	22	19	14	8	2
iAMP21	29	21	14	6	1	0
MLL translocations	30	20	16	14	9	1
Abnormal17p	19	15	9	8	7	2
13q loss	25	19	17	15	9	4
Other	656	573	487	446	268	107



Number at risk

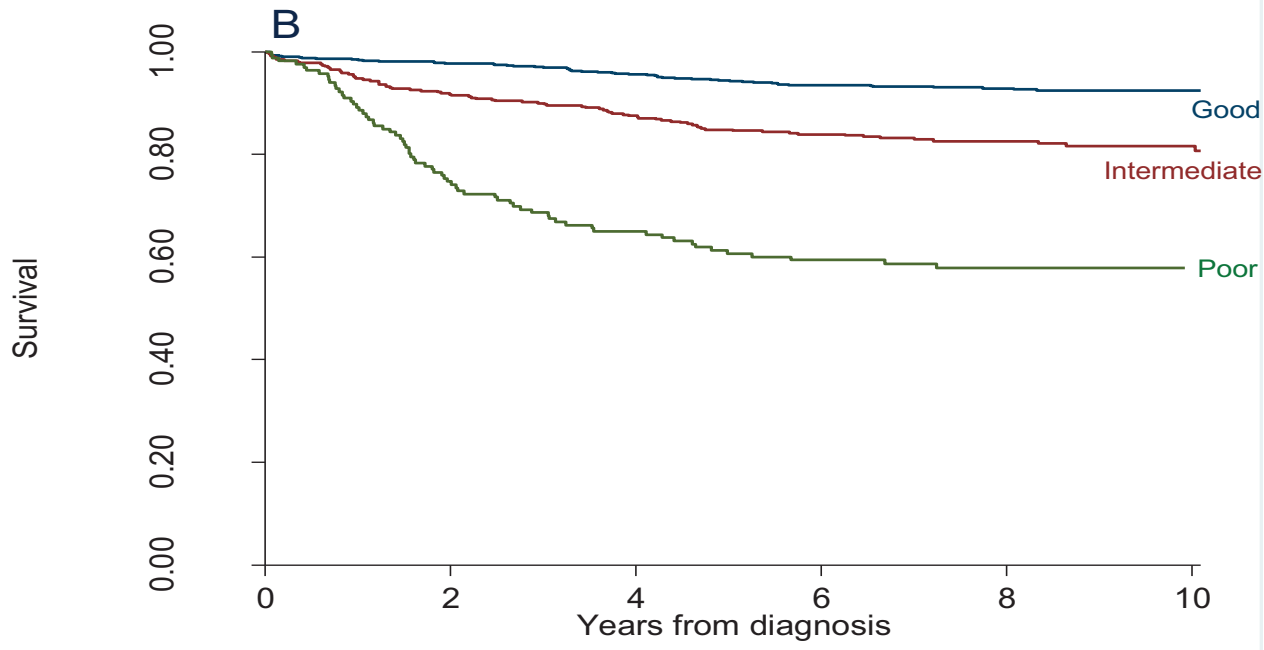
Good	923	891	807	740	424	153
Intermediate	458	405	348	319	192	79
Poor	166	107	82	64	38	10

Supplementary figure 2: Kaplan Meier graphs showing the overall survival for (a) individual chromosomal abnormalities that were significant in univariate analysis, (b) cytogenetic risk groups. NB. For the purposes of drawing this graph patients were classified hierarchically in the order *ETV6-RUNX1*, t(9;22), *MLL* translocations, iAMP21, high hyperdiploidy, abnormal 17p, loss of 13q.



Number at risk

(HeH) High hyperdiplody	555	540	521	485	289	116
ETV6-RUNX1	368	360	351	332	195	65
t(9;22)(q34;q11)	43	29	24	22	13	3
iAMP21	29	24	21	15	9	2
MLL translocations	30	25	21	16	11	1
Abnormal17p	19	15	12	9	8	2
13q loss	25	21	20	19	11	6
Other	656	594	547	502	308	126



Number at risk

Good	923	900	872	817	484	181
Intermediate	458	420	392	358	218	90
Poor	166	124	106	88	56	15

Supplementary figure 3: Kaplan Meier graphs showing relapse-free survival for high hyperdiploid patients with and without (A) triple trisomy (+4,+10,+17) and (B) trisomy 18 .