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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

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ABSTRACT

Diagnostic karyotype provides the framework for risk-stratification schemes in acute myeloid leukemia (AML); however, the prognostic significance of many rare recurring cytogenetic abnormalities remains uncertain. We studied outcome of 5,876 patients (16-59 years), classified into 54 cytogenetic subgroups, treated in the Medical Research Council trials. In multivariable analysis, t(15;17)(q22;q21), t(8;21)(q22;q22) and inv(16)(p13q22)/t(16;16)(p13;q22) were the only abnormalities found to predict a relatively favorable prognosis ($p<10^{-12}$). In patients with t(15;17) treated with extended ATRA and anthracycline-based chemotherapy, additional cytogenetic changes did not impact on prognosis. Similarly, additional abnormalities did not have a significant adverse effect in t(8;21) AML. Whereas in patients with inv(16), presence of additional changes, particularly +22, predicted a better outcome (p=0.004). In multivariable analyses, various abnormalities predicted a significantly poorer outcome, namely: abn(3q) [excluding t(3;5)(q25;q34)], inv(3)(q21q26)/t(3;3)(q21;q26), add(5q)/del(5q), -5, -7, add(7q)/del(7q), t(6;11)(q27;q23), t(10;11)(p11~13;q23), other t(11q23) [excluding t(9;11)(p21~22;q23) and t(11;19)(q23;p13)], t(9;22)(q34;q11), -17 and abn(17p). Patients lacking the aforementioned favorable or adverse aberrations, but with four or more unrelated abnormalities also exhibited a significantly poorer prognosis (designated “complex” karyotype group). These data allow more reliable prediction of outcome for patients with rarer abnormalities and may facilitate development of consensus in reporting of karyotypic information in clinical trials involving younger adults with AML. This study was registered at www.isrctn.org as ISRCTN55678797 and ISRCTN17161961.

INTRODUCTION

Diagnostic karyotype is one of the most powerful independent prognostic indicators in acute myeloid leukemia (AML), which serves to identify biologically distinct subsets of disease and has been widely adopted to provide the framework for risk-adapted treatment approaches (reviewed [1-3]). Large multicenter studies have consistently reported that acute promyelocytic leukemia (APL) patients with the t(15;17)(q22;q21)/*PML-RARA* treated on all-*trans*retinoic acid (ATRA) and anthracycline-based protocols and core binding factor (CBF) leukemias with t(8;21)(q22;q22)/*RUNX1-RUNX1T1* or inv(16)(p13q22)/t(16;16)(p13;q22)/*CBFB-MYH11* receiving intensive chemotherapy involving cytarabine at a range of doses are associated with a relatively favorable outcome, while conversely AMLs with abnormalities of 3q [abn(3q)], deletions of 5q [del(5q)], monosomies of chromosome 5 and/or 7 (-5/-7) or complex karyotype are associated with very poor prognoses[4-10]. However, there has been little consensus as to the outcome of cases with rare recurring cytogenetic abnormalities (i.e. individual incidence <2%) which together account for approximately 10% of AML and have variably been considered to predict an intermediate or adverse prognosis[4-10]. Further sources of inconsistency between cytogenetic classification systems adopted by different trial groups relate to the prognostic impact of additional abnormalities in patients with favorable karyotype, particularly accompanying the t(8;21), the outcome of translocations involving the *MLL* locus at 11q23 and the level of cytogenetic complexity considered to confer adverse risk. Moreover, a recent study involving 1,975 adults (aged 15-60 years) with AML has suggested the existence of a novel adverse risk group characterized by the presence of an autosomal monosomy in conjunction with at least one other autosomal monosomy or structural abnormality (denoted monosomal karyotype positive, MK+)[11].

In the hierarchical Medical Research Council (MRC) cytogenetic classification system developed over a decade ago, that was based on the analysis of a cohort of 1,612 children and younger adults (<55 years) treated in the MRC AML10 trial, three cytogenetic risk groups were distinguished[4]. Patients with t(15;17), t(8;21) and inv(16) irrespective of the presence of additional cytogenetic changes were assigned to the “Favorable Risk” group; patients lacking any of these aberrations and found to have abn(3q), del(5q), -5/-7 or complex karyotype (i.e. 5 or more unrelated cytogenetic

abnormalities) were defined as “Adverse Risk”. The remaining patients, i.e. those with normal karyotype and other structural or numerical abnormalities comprised the “Intermediate Risk” group. In the original MRC study infrequent abnormalities that were present in less than 20 patients were not considered individually and were assigned to the intermediate risk group; however, it was recognized that there was likely to be considerable heterogeneity in clinical outcome according to the nature of these rare cytogenetic entities, of relevance in informing clinical management and the development of more appropriate risk-stratified treatment approaches for such patients. To begin to address this issue and with the aim of further refining cytogenetic classification of AML which could ultimately facilitate comparison of clinical trial data from different groups, we considered impact of karyotype on outcome in a much larger cohort of younger adult patients treated in the MRC trials.

PATIENTS AND METHODS

Patients

The study cohort comprised 5,876 AML cases with successful karyotype analysis enrolled in successive MRC trials conducted between May 1988 and January 2009: AML10 (1988-1995, n=1,238), AML12 (1995-2002, n=2,241) and AML15 (2002-2009, n=2,397), including 435 cases with secondary AML. The median age of the patients was 44 years (range 16-59). AML was diagnosed and classified according to the FAB classification in the AML10 and AML12 trials; in AML15 the revised diagnostic criteria of the WHO classification[12] were adopted. Sample collection and analyses was approved by the Multicenter Research Ethics Committee for Wales.

Therapy

All patients received intensive anthracycline and cytarabine (Ara-C) based combination chemotherapy. Details of the AML10 treatment protocol have been published previously; briefly, patients were randomized to receive induction therapy with two courses of DAT (daunorubicin, Ara-C, 6-thioguanine: course 1, DAT 3+10; course 2, DAT 3+8) or ADE (Ara-C, daunorubicin, etoposide: course 1, ADE 10+3+5; course 2, ADE 8+3+5)[13]. The third and fourth courses of consolidation chemotherapy comprised MACE (m-amsacrine,

Ara-C, etoposide) and MidAC (mitoxantrone, Ara-C), respectively. This trial investigated the role of autologous and allogeneic bone marrow transplantation (BMT) following this intensive therapy, as described[14,15].

AML12 was based on the marginally better induction regimen from AML 10 (ADE) and the standard treatment template became ADE, ADE, MACE, MidAC. AML12 investigated whether mitoxantrone might be superior to and less cardiotoxic than daunorubicin, by comparing ADE with MAE (mitoxantrone, Ara-C, etoposide)[16,17]. AML10 risk group stratification was applied in AML12 for the delivery of risk-directed therapy[18], with allogeneic transplant in first complete remission being restricted to standard and adverse risk patients and autologous transplant was not a treatment option. After recruitment of 1,658 patients to the ADE versus MAE randomization, the induction schedule was changed to compare two dose levels of Ara-C (200 vs 100mg/m^2 given twice daily) in a DAT schedule with or without ATRA. All patients in AML12 were eligible for randomization to receive 4 versus 5 courses of treatment, where for standard and adverse risk adults the final course could be either chemotherapy or stem cell transplant (allogeneic for patients with a sibling donor, autologous otherwise). The additional course of treatment was ICE (Idarubicin 10mg/m^2 d1-3; Cytarabine 100mg/m^2 d1-5 every 12h; Etoposide 100mg/m^2 d1-5).

In AML15, adult patients who did not have APL were randomized to receive ADE (as given in AML10 and AML12), DA (course 1, DA 3+10: Daunorubicin 50 mg/m^2 d1,3,5; Ara-C 100 mg/m^2 d1-10 every 12h; course 2, DA 3+8: Daunorubicin 50 mg/m^2 d1,3,5; Ara-C 100 mg/m^2 d1-8 every 12h) or FLAG-Ida (course 1, Fludarabine 30 mg/m^2 d2-6; Ara-C 2g/m^2 d2-6; G-CSF 263μg d1-7; Idarubicin 8 mg/m^2 d4,5,6; course 2, idem). Patients were also randomized to receive gemtuzumab ozogamicin (3mg protein/m^2) or not on day 1 of course 1. After recruitment of 1,113 patients, the gemtuzumab ozogamicin randomization in induction was discontinued and patients with FLT3 mutant AML were randomized to receive or not lestaurtinib after each of the first 4 treatment courses. Patients with standard or poor risk disease with an available donor were eligible for transplant. Standard allograft was given as course 3; for patients over 45 years a mini-allograft was recommended and given as course 4 after MACE consolidation. The remaining patients were randomized to standard MRC consolidation chemotherapy (MACE + MidAC) or high-dose cytarabine, at doses of either 1.5 g/m^2 or 3.0 g/m^2, with a

sub-randomization to give gemtuzumab ozogamicin (3mg protein/m^2) or not on day 1 of course 3 (excluding those patients receiving lestaurtinib). Patients were also randomized to receive or not a fifth course i.e. cytarabine at a dose of 1.5 g/m^2; following the early results of AML12, this randomization was restricted to younger patients only (aged <45).

From January 1993, patients with APL were eligible for the MRC ATRA trial, and were randomized to receive either short or extended courses of ATRA, in combination with induction chemotherapy as per the AML 10/12 protocol[19]. After the closure of the MRC ATRA trial (January 1997), patients with APL entered into AML12 routinely received an extended course of ATRA commenced simultaneously with induction chemotherapy and continued until achievement of morphological remission (to a maximum of 60 days) followed by MRC combination chemotherapy. In AML15, the MRC treatment schedule used in AML12 was compared with a PETHEMA schedule. In addition, patients were randomized to receive gemtuzumab ozogamicin or not on day 1 of course 3, as described[20].

Cytogenetics

Cytogenetic analysis was performed on metaphases from bone marrow (BM) aspirates taken at diagnosis, using standard procedures. This was carried out in the regional cytogenetics laboratories, whose satisfactory performance was monitored by a national external quality assurance scheme: UK National External Quality Assessment Service (NEQAS) for Clinical Cytogenetics[21]. Karyotypes were entered into the Leukaemia Research, UK Cancer Cytogenetics Group Karyotype Database in Acute Leukaemia[22], as well as the clinical trials database. Patients were classified as having an abnormal, normal or failed cytogenetic result. A result was regarded as normal following analysis of 20 or more normal metaphases. Analysis of less than 20 normal metaphases was regarded as a fail. 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)[23] and classified according to the presence of the chromosomal abnormalities shown in Table 1. According to this scheme, abnormal karyotypes with more than one abnormality were classified into a number of relevant groups. Cases with none of these changes were classified as “other”. Karyotype

complexity was defined by the number of unrelated abnormalities present from 1 to 5 or more. A balanced translocation e.g. t(8;21)(q22;q22) was defined as a single abnormality, as the two events leading to it are related. Trisomy and monosomy were regarded as single abnormalities. Two abnormalities included the gain of two chromosomes, even if they were the same, or the gain of a derived chromosome. Unbalanced translocations leading to gain and loss of chromosomal material e.g. der(7)t(1;7)(q21;q22) were also counted as two abnormalities.

Endpoints and statistics

Outcome data were analyzed in patients with recurring cytogenetic abnormalities occurring in at least 20 patients across the three trials. Patients were defined as having a complete response (CR/CRi) if they exhibited a normocellular BM aspirate containing <5% leukemic blasts and showed evidence of normal maturation of other marrow elements. Remission failures were classified by the investigating clinician as due to induction death (ID) (death related to treatment and/or hypoplasia within 30 days), or resistant disease (RD) (failure to eliminate disease, including partial remissions). Where clinician evaluation was not available, deaths within 30 days were deemed ID and other failures RD. The following definitions are also used: overall survival (OS) is the time from randomization to death. For remitters, relapse free survival (RFS) is the time from CR/CRi to first event (relapse or death in CR); cumulative incidence of relapse (CIR) is the cumulative probability of relapse with death in CR as competing risk. OS/RFS/CIR percentages are quoted at 10 years. Surviving patients were censored on 26th October 2008 (AML10,12) or 1st January 2009 (AML15) when follow-up was complete for 97% of patients (the small number of patients lost to follow-up are censored at the date they were last known to be alive). Median follow-up was 7.3 years (range 0.1-20.5 years). There was some difference in outcome between patients with cytogenetic data and those with either failed samples or no sample (10 year OS: with cytogenetics 40% v failed 46% v no sample 34%); after adjustment for age, white blood cell count (WBC), secondary disease and performance status, the difference remained significant ($p<0.0001$).

Demographics, remission rates and reasons for failure to achieve CR were compared using chi-squared and Mantel-Haenszel tests. Kaplan-Meier life-tables were constructed

for time to event and unstratified comparisons were made using the log-rank test. Outcomes of patients with particular abnormalities were compared with the normal karyotype group. Odds ratios (OR) with standard errors (SE) were calculated. All p-values were two-tailed. To allow for multiple testing, the level of significance was set at $p<0.01$ and 99% confidence intervals (CI) were presented for effect sizes. Multivariate modeling was carried out using logistic and Cox regression analyses with a forward selection method. All multivariate analyses had as candidate variables the cytogenetic abnormalities listed in Table 1, after adjustment for other well known prognostic variables, including age, WBC, type of AML (*de novo*/secondary), with performance status as defined by the WHO and clinical trial (AML10/AML12/ AML15) as covariates. P-values were those for entry to the model using the deviance statistic; Wald confidence intervals were used. Throughout the analyses, OR greater than 1 indicated a worse outcome for the abnormality under consideration.

RESULTS

Distribution of cytogenetic abnormalities in younger adults with AML

Overall 2,432 of 5,876 (41%) of patients had a normal karyotype; frequencies of the various cytogenetic abnormalities identified in the remaining patients are shown in Table 1. Together, recurrent balanced chromosomal abnormalities that are the cytogenetic hallmarks of genetically defined disease entities in the revised WHO classification[24] were identified in 28% of cases, namely t(15;17)(q22;q21) (13%), t(8;21)(q22;q22) (7%), inv(16)(p13q22)/t(16;16)(p13;q22) (5%), t(6;9)(p23;q34) (1%), t(9;11)(p21~22;q23) (1%) and inv(3)(q21q26)/t(3;3)(q21;q26) (1%). These abnormalities were confirmed to be mutually exclusive (Supplementary Table 1). In patients lacking one of the above-mentioned recurrent genetic abnormalities; 750 (18%) harbored particular cytogenetic abnormalities that have been collectively designated as “MDS-related” in the 2008 WHO classification. “MDS-related” unbalanced abnormalities were present in 711 cases [-7/del(7q) n=336, -5/del(5q) n=258, i(17q)/t(17p) n=104, -13/del(13q) n=97, del(11q) n=109, del(12p)/t(12p) n=88, del(9q) n=69, idic(X)(q13) n=4] and balanced abnormalities were identified in 42 cases [t(11;16)(q23;p13) n=2, t(3;21)(q26;q22) n=9, t(1;3)(p36;q21)

n=2, t(2;11)(p21;q23) n=1, t(5;12)(q33;p12) n=2, t(5;7)(q33;q11) n=1, t(3;5)(q25;q34) n=25]. There were significant differences in the distribution of cytogenetic abnormalities with respect to age, with balanced rearrangements t(3;5)(q21~25;q31~35), t(8;21)(q22;q22), t(15;17)(q22;q21), inv(16)(p13q22) and t(11q23) typically occurring in younger patients, whereas unbalanced abnormalities including various monosomies, del(5q), del(7q) and trisomies of chromosome 11 and 13 were over-represented in older patients (Table 1). We also undertook a systematic analysis to establish which abnormalities tend to coexist, revealing a number of significant associations (see Supplementary Table 1).

Impact of cytogenetic abnormalities on disease outcome

For analysis of patient outcomes, those with the t(15;17) who were not confirmed as receiving a long ATRA treatment regimen were excluded from all analyses (n=181). In comparison to normal karyotype, a considerable number of cytogenetic abnormalities were predictive of disease outcome with respect to response to induction therapy, risk of relapse and overall survival, both in univariate analysis and after adjustment for age, WBC, secondary disease and performance status (Table 2). Accordingly, significant differences in survival were observed amongst the cytogenetic entities specified in the 2008 WHO Classification (Figure 1).

Significance of additional cytogenetic abnormalities in CBF leukemias

To address previous inconsistencies in the risk group assignment of t(8;21) associated CBF leukemia based on the presence of particular additional abnormalities (e.g. deletions of the long arm of chromosome 9 [del(9q)])[25] and karyotype complexity[26], this was investigated in a cohort of 421 patients. No significant difference in OS was observed according to whether the t(8;21) was accompanied by del(9q) or the presence of additional abnormalities, as compared to those with t(8;21) alone (Supplementary Figure 1a,b). Loss of an X chromosome had no impact on outcome, although loss of the Y chromosome in males was associated with a trend (p=0.04) for better overall survival (Supplementary Figure 1c,d). In patients with inv(16)/t(16;16), presence of any additional abnormality was associated with a significantly better outcome, with patients with an additional chromosome 22 having a particularly favorable prognosis (Supplementary Figure 2a,b). However, it should be noted that those patients with an additional

chromosome 22 had a significantly lower presenting WBC compared to those with inv(16)/t(16;16) alone (median 18.9 (range 1.6-224.2) vs median 44.6 (range 1.5-370.0), p<.0001).

Significance of additional cytogenetic abnormalities in t(15;17) and other aberrations specified in the 2008 WHO classification

Amongst the cohort of 607 patients with t(15;17) treated with extended ATRA and anthracycline-based chemotherapy, the presence of additional abnormalities had no significant impact on outcome, with all subsets showing a relatively favorable outcome. This included patients in which the t(15;17) was accompanied by abnormalities of 17p or karyotypic changes which in their own right would have been considered adverse according the original MRC classification[4] (Supplementary Figure 3a,b,c). We also considered the impact of additional cytogenetic abnormalities in patients with the other recurrent balanced rearrangements recognized by the WHO classification. These did not influence outcome in patients with t(9;11)(p21~22;q23) (Supplementary Figure 4). Patients with inv(3)/t(3;3) had a dismal prognosis irrespective of the presence of monosomy 7 (Supplementary Figure 5). The t(6;9)(p23;q34) typically occurred as the sole cytogenetic abnormality and showed a trend to poorer outcome (Table 2), with a 10 year survival of 27% (p=0.04 in adjusted analyses).

Refining cytogenetic risk group classification in younger adults with AML

Multivariable analyses were conducted to identify karyotypic abnormalities with independent prognostic significance, taking into account age, presenting WBC, performance status and type of AML (*de novo*/secondary). The t(15;17), t(8;21) and inv(16)/t(16;16) were the only abnormalities that were predictive of significantly better outcome ($p<10^{-12}$). After exclusion of this favorable prognostic group, Cox regression analyses revealed various abnormalities that were independently predictive of a significantly poorer outcome (Table 3). The impact of karyotype complexity on outcome in patients without favorable features was investigated after adjustment for the abnormalities with independent prognostic significance in multivariable analysis (i.e. any of the aberrations specified in Table 3). Patients with 4 or more unrelated abnormalities exhibited a significantly poorer prognosis (HR 1.58 (1.29-1.94) p<.0001) and this was

seen in the effect of complexity on patients lacking any of the prognostically significant abnormalities (i.e. t(15;17), t(8;21), inv(16)/t(16;16) and those in Table 3; Figure 2)

Results of the multivariable analysis conducted in this large study cohort were used to further refine the original MRC cytogenetic classification (Table 4). Although statistically significant, presence of the +8 abnormality did not lead to poor outcomes and this was therefore not included in the revised definition (Supplementary Figure 6). Application of the revised classification scheme led to reassignment of 299 cases (i.e. 15% of the 1951 with abnormal karyotype, excluding those with t(15;17) and CBF leukemia); 275 cases moved from intermediate to adverse and conversely 24 (i.e. those with t(3;5) without additional adverse features) were transferred from the adverse to the intermediate risk group (Figure 3, Supplementary Figure 7a,b).

Impact of NPM1 and FLT3-ITD mutation status in patients with refined intermediate risk cytogenetic abnormalities

Molecular genetics is increasingly being used to risk stratify AML in conjunction with conventional cytogenetics, with many previous studies focusing on the prognostic impact of molecular markers in AML with normal karyotype[3,27]. We wished to investigate the impact of nucleophosmin (NPM1) and Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutations on outcome in the cohort of patients with cytogenetic abnormalities defined as intermediate risk according to the refined MRC classification (see Table 4). Genotyping information was available from 215 AML patients from this group[28]; in accordance with the findings of previous studies in normal karyotype AML (reviewed [3,27]), presence of FLT3-ITD with wild type NPM1 predicted a poor prognosis, while NPM1 mutation in the absence of FLT3-ITD was associated with a reduced risk of relapse with improved overall survival (Supplementary Figure 8a,b). Sample sizes were too small to address the prognostic impact of CEBPA mutations in this group, or of NPM1 and CEBPA mutation status within the cohort of patients with adverse risk cytogenetic abnormalities.

Relationship between cytogenetic risk groups and monosomal karyotype

Finally we considered the distribution of cases with monosomal karyotype (designated MK+) as defined by Breems et al[11] within the original and revised MRC cytogenetic classification systems. The vast majority of cases with monosomal karyotype (318/338, 94%) fell within the original MRC adverse risk group (accounting for 45% of this group), with only 20 cases assigned to the intermediate risk group, and were confirmed to have a very poor prognosis (Supplementary Figure 9a). Application of the revised MRC classification (Table 4), led to reassignment of a further 13 MK+ cases to the adverse risk group. While the outcome of MK+ cases was noted to be particularly poor (5% OS at 10 years), the overall survival of patients with adverse karyotype as defined in the revised MRC classification and lacking a monosomal karyotype was also extremely low (OS 16%, Supplementary Figure 9b).

DISCUSSION

Diagnostic karyotype is a major prognostic indicator in AML, which is widely used in conjunction with information on NPM1, FLT3 and CEBPA mutation status particularly for cases with normal karyotype as the basis for directing risk-adapted treatment approaches[3,27]. Nevertheless, informed clinical decision making in situations in which cytogenetic analysis shows rarer karyotypic abnormalities has been hampered by a lack of consensus regarding the likely outcome of such patients. Discrepancies in risk group assignment of these cases according to commonly applied cytogenetic classification systems most likely reflect limitations imposed by small sample sizes that have rendered the outcome data unreliable. Further confounding factors include variations in inter- and intra-study treatment approach, as well as differences in the patient population, particularly with respect to age distribution[1]. Despite these limitations, it would be helpful if greater standardization in risk-stratification in AML could be achieved, as a means of optimizing therapy and also for reporting outcome data, thereby enabling more reliable comparison of results from different international trial groups. Apart from the benefit of achieving greater consensus in cytogenetic classification, establishing the outcome associated with rarer cytogenetic abnormalities is important, particularly given the results of a recent meta-analysis that has suggested that a relapse risk in excess of 35% can

provide a useful working threshold to identify patients in whom allogeneic transplant may confer a survival benefit[10].

In order to refine existing cytogenetic classification systems we examined the prognostic significance of rarer abnormalities drawn from a large series of 5876 adult patients aged 16-59 years, receiving comparable therapy. In multivariable analyses, t(15;17), t(8;21) and inv(16)/t(16;16) emerged as the only abnormalities conferring a relatively favorable prognosis. Amongst APL patients with the t(15;17), treated with standard ATRA and anthracycline-based protocols, the presence of additional cytogenetic abnormalities (irrespective of the nature or complexity) had no significant impact on prognosis (Supplementary Figure 3), which is in accordance with data from large European APL Group and PETHEMA studies[29,30]. This would suggest that an adverse impact on outcome from the presence of additional abnormalities reported previously[31] may have been ameliorated by optimal ATRA and anthracycline-based therapy or reflect a chance effect associated with smaller sample size. Based on an analysis of 421 patients, we also found that particular additional cytogenetic abnormalities did not adversely affect outcome in t(8;21) CBF leukemia, in contrast with previous reports that suggested a negative impact for del(9q)[25], complex karyotype[26] or loss of –Y chromosome in males[32]. Indeed, we noted a trend (p=0.04) to more favorable survival in the latter group (Supplementary Fig 1d). However, our data are in accordance with those of CALGB[33] and the German AML Intergroup[32] with respect to the prognostic significance of additional abnormalities in patients with inv(16), showing that presence of +22 predicts a significantly better outcome (Supplementary Figure 2b). The reasons for this difference remain to be established; however, a previous study has suggested that this cannot solely be accounted for by KIT mutation status[34]. Patients with inv(16) as the sole abnormality were noted to have significantly higher WBC[32] and defining the mechanisms underlying this may provide insights into the higher risk of relapse.

Having excluded cases with favorable karyotype (i.e. t(15;17), t(8;21), inv(16)/t(16;16)), multivariable analyses, conducted on the enlarged MRC data set showed that a number of cytogenetic abnormalities were independent predictors of a poor prognosis (Table 3). These included t(3;3)/inv(3), del(5q)/-5, and -7 that were recognized as adverse risk factors in the original MRC classification[4]. However, a number of abnormalities that were too infrequent to be considered previously were also found to be independent predictors

of poor outcome. These included -17 and abnormalities of 17p which are associated with loss of *TP53*[35], and t(9;22)(q34;q11) which has been associated with poor prognosis in a large case series[36], leading to the assignment of these entities to the adverse risk group in a number of existing cytogenetic classification systems[5,8,9]. Abnormalities of 3q and 5q are also generally considered as adverse prognostic indicators; however, we found that the outcome of the t(3;5) which is associated with formation of the NPM1-MLF1 fusion[37], and considered an MDS-related abnormality in the 2008 WHO classification[24], did not differ significantly from patients with normal karyotype; although we recognize that the number of cases with t(3;5) was relatively small and this should be confirmed in a larger patient cohort. Other WHO 2008 specified MDS-related abnormalities were associated with a poor prognosis, even when cases with -5/del(5q) and -7 were excluded (Figure 1).

The overall outcome for patients with t(11q23) was significantly worse than for those with normal karyotype (adjusted HR for survival 1.77 (1.42-2.23) p<0.00001). However, the chromosomal partner was observed to have an important bearing upon prognosis. The t(9;11)(p21~22;q23) which leads to the *MLLT3-MLL* fusion, and which is now recognized as a distinct disease entity in the WHO classification[24], was found to have a relatively favorable outcome, in accordance with the majority of studies[38-41]. A similar outcome was observed in patients with t(11;19)(q23;p13), although the involved fusion partner (i.e. *ELL* or *MLLT1* (*ENL*), located at 19p13.1 and 13.3, respectively)[42] was not distinguished in this study. In multivariable analysis, cases with t(6;11)(q27;q23) and t(10;11)(p12;q23), involving *MLLT4* (*AF6*) and *MLLT10* (*AF10*) genes respectively[42] predicted a very poor prognosis. Interestingly, both of these abnormalities have been associated with a poor prognosis in previous studies[43-47] including a recent large international pediatric study considering 756 cases of AML with *MLL* translocations[47]. In the latter study, the most favorable outcome was observed in cases with t(1;11)(q21;q23); although this abnormality was too infrequent in our series (n=3) to consider its prognostic significance in adults. Our data are also in agreement with a large German study involving 180 adults with 11q23 translocations, reported by Krauter and colleagues[41], in which t(9;11) and t(6;11) were found to have a relatively favorable and adverse outcome, respectively in multivariable analysis. In contrast to our data, t(11;19) and t(10;11) did not emerge as independent prognostic factors in the German study, but were each identified in less than 20 cases.

Another disease entity recognized in the updated WHO classification is the t(6;9)/*DEK-CAN* [24], which was associated with a very poor prognosis in a large case series[48] and is generally assigned to the adverse cytogenetic risk group[1,2]. The poor outcome may relate to a strong association with FLT3-ITD mutations[49]. In the present study, there was some evidence of poorer survival in patients (n=42) with the t(6;9)(p23;q34) as compared to those with normal karyotype (27% vs 38%, adjusted HR 1.55 (0.88-2.74) p=0.04), but this effect was not sufficiently strong to emerge in multivariable analysis.

The level of karyotypic complexity that confers adverse prognosis provides a further source of inconsistency between cytogenetic classification schemes, with all groups with the exception of the MRC, adopting 3 or more (3+) abnormalities. Accordingly, the latest WHO classification has defined a complex karyotype as one with three or more unrelated abnormalities in the absence of t(15;17), t(8;21), inv(16)/t(16;16) or t(9;11), which, when present, denotes a case as "MDS-related" AML[24]. Based on this definition, the outcome according to karyotype complexity was as follows: (2+:CIR 65%, OS 12%; 3+: CIR,67% OS 10%; 4+: CIR 72%, OS 8%; 5+: CIR 74%, OS 6%, p<.0001 for trend over number of abnormalities on CIR, OS). However, such a definition does not take into account the impact of cytogenetic entities that would confer adverse risk in their own right. Since complex karyotype is widely considered as a predictor for very poor outcome, and frequently used as an indication for allogeneic transplantation or experimental treatment approaches it is critical that the definition of this entity is robust. Therefore, we investigated the impact of karyotype complexity on outcome in patients with particular cytogenetic abnormalities that would, in their own right, have led to their assignment to the intermediate or adverse risk groups, respectively, disregarding the number of unrelated abnormalities. Level of karyotype complexity was observed to have little impact on outcome in patients already having at least one of the independent adverse risk abnormalities identified on multivariable analysis, who, generally, had a very poor prognosis. Conversely, in patients lacking any of these independent adverse risk abnormalities, t(15;17), CBF leukemia or t(9;11), the presence of 4 or more unrelated changes was found to provide the most informative cut-off, predicting a significantly poorer prognosis even after adjustment for abnormalities known to be prognostic (HR 1.60 (1.31-1.96) p<.0001).

Analysis of this very large series of AML patients, treated in the MRC trials with prolonged follow-up has allowed the prognostic significance of a number of rarer cytogenetic abnormalities to be established. This has achieved further refinement of the original hierarchical MRC cytogenetic classification scheme and reconciled a number of differences between existing classification systems. This study will hopefully provide impetus facilitating the development of consensus in the reporting of karyotype data, allowing more reliable comparison between clinical trials involving younger adults with AML. We have independently confirmed that the presence of a monosomal karyotype identifies a group of patients with very poor prognosis[11], but note that the majority of such patients fall within the adverse risk group as defined by the MRC. Importantly we have shown that a substantial proportion of patients cannot be reliably classified as having poor risk AML based on the presence of a monosomal karyotype alone.

Our data lend support to the continued use of cytogenetic analysis as a component of the routine diagnostic work-up of AML to provide a framework for risk-stratification, to be used in conjunction with screening for an increasing range of molecular markers - required not only to predict risk of relapse in those with normal karyotype, but also to further dissect out groups of patients with differing prognoses who share particular cytogenetic abnormalities, or fall within the same cytogenetic risk group. For example, we show that NPM1 and FLT3-ITD mutation status provide independent prognostic information in patients who would otherwise have been considered intermediate risk on the basis of the karyotypic abnormalities identified (Supplementary Figure 8a,b), in accordance with a recent study by Haferlach and colleagues[50]. Further refinement of risk groups may be achieved through molecular screening for other mutations including *CEBPA*, *WT1*, *RUNX1*, *MLL-PTD* and over-expression of genes such as *EVI1* (reviewed [3]). A key and ongoing challenge is the integration of pre-treatment parameters, including cytogenetics and an ever-expanding number of molecular markers, with early assessment of treatment response in order to develop robust algorithms that further refine risk stratification of AML in order to guide consolidation therapy.

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AUTHOR CONTRIBUTIONS

DG designed the study and wrote the paper with RKH, AVM and CJH. RKH performed the statistical analyses, AVM and CJH classified the cytogenetic abnormalities and managed the cytogenetics database. HW and SC undertook cytogenetic analyses and coordinated data collection. KW contributed to the design of the MRC AML trials, AHG and AKB contributed to study design and were lead participants in the MRC AML trials. All authors approved the final version of the manuscript. The authors have no relevant financial conflict of interest.

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FIGURE AND TABLE LEGENDS

Figure 1

Impact of cytogenetic entities recognized in 2008 WHO classification[24] on survival.

*: excluding patients with t(15;17), t(8;21), inv(16), t(9;11), t(6;9), inv(3)/t(3;3);

**: excluding patients with any other abnormalities listed above.

Figure 2

Impact of karyotype complexity on survival in patients lacking cytogenetic abnormalities that confer relatively favorable or adverse prognoses in multivariable analysis.

Figure 3

Outcome of patients according to original and refined MRC cytogenetic classification. The patients previously assigned to the “adverse risk” group and reclassified as “intermediate risk” all had t(3;5)(q21~25;q31~35).

Table 1

Frequency and demographics of chromosomal abnormalities

Table 2

Impact of cytogenetic abnormalities on disease outcome as compared to normal karyotype.

Table 3

Cytogenetic entities predicting significantly poorer overall survival in multivariable analysis

* excluding t(9;11)(p21~22;q23), t(11;19)(q23;p13)

Table 4

Revised MRC prognostic classification based on multivariable analyses

Table 1: Frequency and demographics of chromosomal abnormalities

Chromosome/Arm involved	Description of Chromosomal Abnormality	Patients	Age median (range)	Secondary disease (% of those with abnormality)
		No. (%)*		
--	Normal Karyotype	2432 (41)	46 (16-59)	135 (6)
1	Abnormality of 1p	86 (2)	43.5 (16-59) p=0.9	16 (19) p=0.0005
	t(1;22)(p13;q13)	1 (<.5)	37	0
	Abnormality of 1q	84 (1)	48 (16-59) p=0.09	12 (14) p=0.03
3	Monosomy 3	39 (1)	51 (22-59) p=0.002	9 (23) p=0.002
	Abnormality of 3q			
	inv(3)(q21q26)/t(3;3)(q21;q26)	69 (1)	43 (18-59) p=0.7	11 (17) p=0.02
	t(3;5)(q21~25;q31~35)	26 (<.5)	30.5 (16-58) p=0.005	3 (12) p=0.4
	Other abnormality of 3q	108 (2)	46.5 (18-59) p=0.03	16 (15) p=0.008
4	Trisomy 4	70 (1)	43 (18-59) p=0.7	5 (7) p=1.0
5q	Abnormality of 5q			
	Monosomy 5	129 (2)	51 (18-59) p<.0001	24 (19) p<.0001
	del(5q)	146 (2)	51 (16-59) p<.0001	28 (19) p<.0001
	add(5q)	60 (1)	45.5 (18-59) p=0.4	9 (15) p=0.04
6	Trisomy 6	65 (1)	49 (16-59) p=0.03	10 (15) p=0.03
	t(6;9)(p23;q34)	42 (1)	44 (19-59) p=0.5	2 (5) p=0.8
	Abnormality of 6q, not t(6;11)	79 (1)	44 (16-59) p=0.9	9 (11) p=0.19
7	Monosomy 7	279 (5)	47 (16-59) p=0.0005	54 (19) p<.0001
	Abnormality of 7q			
	del(7q)	145 (2)	49 (16-59) p=0.0005	28 (19) p<.0001
	add(7q)	68 (1)	47 (16-59) p=0.02	9 (13) p=0.10
	Abnormality of 7p	81 (1)	42 (16-59) p=0.5	17 (21) p<0.0001
8	Trisomy 8	547 (10)	44 (16-59) p=0.7	57 (10) p=0.008

	t(8;21)(q22;q22) and variants	421 (7)	40 (16-59) p<.0001	13 (3) p=0.0001
	Abnormality of 8p11~12	23 (<.5)	32 (16-58) p=0.05	2 (9) p=0.7
9	Monosomy 9	25 (<.5)	47 (17-57) p=0.4	3 (12) p=0.4
	t(9;22)(q34;q11) and variants Deletion of 9q, including add(9q)	47 (1) 133 (2)	43 (22-58) p=0.7 45 (16-59) p=0.7	1 (2) p=0.3 10 (8) p=0.9
11	Trisomy 11	81 (1)	51 (16-59) p<.0001	7 (9) p=0.7
	All 11q23			
	t(9;11)(p21~22;q23)	61 (1)	38 (16-58) p=0.0003	6 (10) p=0.5
	t(10;11)(p11~14;q13~23)	34 (1)	33.5 (16-59) p<.0001	0 p=0.18
	t(6;11)(q27;q23)	24 (<.5)	33 (17-57) p=0.001	1 (4) p=1.0
	t(11;19)(q23;p13)	30 (1)	35.5 (16-57) p=0.01	4 (13) p=0.3
	other 11q23	62 (1)	38.5 (17-59) p=0.008	7 (11) p=0.2
	Abnormality of 11q (not 11q23)	117 (2)	43 (16-59) p=0.9	9 (8) p=0.9
	Abnormality 11p13~15	37 (1)	40 (16-57) p=0.14	7 (19) p=0.007
12	Abnormality of 12p			
	Monosomy 12	57 (1)	52 (18-59) p<.0001	11 (19) p=0.003
	Other abnormality of 12p13	50 (1)	46 (16-58) p=0.4	4(8) p=0.8
	Other abnormality of 12p, not 12p13	93 (2)	45 (17-59) p=0.4	19 (20) p<.0001
13	Trisomy 13	93 (2)	50 (16-59) p<.0001	12 (13) p-0.07
	Abnormality of 13q			
	Monosomy 13	73 (1)	49 (16-59) p=0.01	14 (19) p=0.0008
	Deletion of 13q	27 (<.5)	42 (20-59) p=0.17	2 (7) p=1.0
15	t(15;17)(q22;q21) and variants	788 (13)	39 (16-59) p<.0001	24 (3) p<.0001
	Abnormality of 15q, not t(15;17)	40 (1)	42.5 (19-58) p=0.4	3 (8) p=1.0
16	inv(16)(p13q22)/t(16;16)(p13;q22)	284 (5)	38 (16-59) p<.0001	12 (4) p=0.04
	Abnormality of 16q, not inv(16)	91 (2)	43 (16-59) p=0.8	12 (13) p=0.04
17	Monosomy 17	121 (2)	51 (16-59) p<.0001	15 (12) p=0.05
	Abnormality of 17p	145 (2)	46 (16-59) p=0.03	20 (14) p=0.006

18	Monosomy 18	97 (2)	49 (18-59) p<.0001	20 (21) p<0.0001
19	Trisomy 19	58 (1)	41 (16-59) p=0.15	4 (7) p=1.0
20	Monosomy 20	53 (1)	49 (16-59) p=0.004	10 (19) p=0.005
	Abnormality of 20q	48 (1)	49 (20-59) p=0.04	4 (8) p=0.8
21	Trisomy 21 (acquired)	148 (3)	46 (17-59) p=0.13	21 (14) p=0.004
	Abnormality of 21q, not t(8;21)	74 (1)	49 (16-59) p=0.004	15 (20) p=0.0003
22	Trisomy 22	113 (2)	42 (18-59) p=0.9	10 (9) p=0.6
X	Loss of X	109 (2)	41 (16-59) p=0.16	9 (8) p=0.7
Y	Loss of Y	200 (3)	42 (16-59) p=0.4	10 (5) p=0.2
Other**		139 (2)	46 (16-59) p=0.05	14 (10) p=0.2
Level of Karyotype Complexity	1 Abnormality	1830 (31)	42 (16-59)	131 (7)
Complexity	2 Abnormalities	786 (13)	40 (16-59)	70 (9)
	3 Abnormalities	275 (5)	41 (17-59)	17 (6)
	4 Abnormalities	123 (2)	42 (16-59)	14 (11)
	5 or More Abnormalities	430 (7)	49 (16-59) p=0.09 for trend	68 (16) p<.0001 for trend

*as percentage of cases with a successful cytogenetic result

**other karyotypes, not classified into any listed group

Cases were categorized according to presence of the cytogenetic entities previously defined in a large cohort of pediatric AML patients treated in the MRC AML trials[22]. According to this scheme, abnormal karyotypes with more than one abnormality were classified into a number of relevant groups.

Table 2: Impact of cytogenetic abnormalities on disease outcome as compared to normal karyotype.

Chromosome/ Arm involved	Description of Chromosomal Abnormality	Complete remission (CR)‖			Overall Survival (OS)			Cumulative Incidence of Relapse (CIR)		
		Rate	Unadjusted OR, 99% CI, p-value*	Adjusted OR, 99% CI, p-value*	10 year OS	Unadjusted HR, 99% CI, p-value†	Adjusted HR, 99% CI, p-value‡	10 year CIR	Unadjusted HR, 99% CI, p-value†	Adjusted HR, 99% CI, p-value‡
--	Normal Karyotype	90%			38%			49%		
1	Abnormality of 1p†	68%	4.13 (2.21-7.71) p<.0001	5.51 (2.81-10.80) p<.0001	20%	2.58 (1.64-4.05) p<.0001	2.20 (1.57-3.08) p<.0001	58%	1.64 (0.93-2.91) p=0.03	1.62 (1.01-2.60) p=0.008
	Abnormality of 1q†	63%	5.19 (2.82-9.55) p<.0001	5.78 (3.02-11.07) p<.0001	21%	2.26 (1.45-3.54) p<.0001	1.88 (1.33-2.65) p<.0001	55%	1.26 (0.72-2.19) p=0.3	1.30 (0.78-2.15) p=0.19
3	Monosomy 3	46%	10.16 (4.36-23.65) p<.0001	12.11 (5.02-29.19) p<.0001	3%	24.46 (10.01-59.76) P<.0001	4.20 (2.68-6.58) p<.0001	82%	75.92 (17.15-336.0) p<.0001	5.17 (2.68-9.96) p<.0001
	Abnormality of 3q									
	inv(3)(q21q26)/t(3;3)(q21;q26)‡	36%	15.33 (7.86-29.88) p<.0001	19.80 (9.79-40.07) p<.0001	3%	13.22 (7.14-24.48) p<.0001	4.07 (2.89-5.72) p<.0001	89%	14.41 (4.64-44.74) p<.0001	4.04 (2.22-7.36) p<.0001
	t(3;5)(q21~25;q31~35)‡	96%	0.36 (0.03-5.06) p=0.3	0.44 (0.03-6.51) p=0.4	34%	1.38 (0.66-2.90) p=0.3	1.41 (0.72-2.77) p=0.18	52%	1.46 (0.61-3.50) p=0.3	1.53 (0.72-3.25) p=0.14
	Other abnormality of 3q	59%	6.08 (3.56-10.38) p<.0001	6.98 (3.97-12.25) p<.0001	11.3	5.20 (3.32-8.14) p<.0001	2.77 (2.08-3.68) p<.0001	71%	5.21 (2.70-10.05) p<.0001	2.71 (1.79-4.09) p<.0001
4	Trisomy 4‡	87%	1.31 (0.51-3.33) p=0.5	1.55 (0.57-4.24) p=0.3	16%	1.15 (0.74-1.80) p=0.4	1.23 (0.80-1.88) p=0.2	54%	1.09 (0.64-1.83) p=0.7	1.13 (0.68-1.87) p=0.5
5q	Abnormality of 5q‡									
	Monosomy 5	57%	6.56 (4.02-10.72) p<.0001	7.58 (4.49-12.80) p<.0001	0%	20.31 (12.70-32.47) p<.0001	4.33 (3.35-5.61) p<.0001	75%	16.98 (8.42-34.23) p<.0001	3.80 (2.59-5.57) p<.0001
	del(5q)	58%	6.22 (3.90-9.93) p<.0001	7.28 (4.40-12.06) p<.0001	12%	5.14 (3.47-7.62) p<.0001	2.90 (2.23-3.76) p<.0001	64%	3.02 (1.75-5.19) p<.0001	2.19 (1.47-3.27) p<.0001
	add(5q)	53%	7.62 (3.83-15.17) p<.0001	10.38 (4.96-21.72) p<.0001	10%	10.49 (5.34-20.60) p<.0001	3.58 (2.42-5.30) p<.0001	64%	6.05 (2.25-16.28) p<.0001	2.84 (1.53-5.26) p<.0001
6	Trisomy 6†	78%	2.44 (1.10-5.41) p=0.004	2.52 (1.11-5.73) p=0.003	21%	2.34 (1.40-3.92) p=0.0001	1.88 (1.28-2.76) p<.0001	62%	2.12 (1.12-4.01) p=0.005	1.75 (1.08-2.85) p=0.003
	t(6;9)(p23;q34)‡	88%	1.18 (0.34-4.06) p=0.7	1.65 (0.47-5.82) p=0.3	27%	1.47 (0.77-2.81) p=0.14	1.55 (0.88-2.74) p=0.04	62%	1.70 (0.76-3.79) p=0.10	1.61 (0.82-3.16) p=0.06
	Abnormality of 6q, not t(6;11)†	63%	5.05 (2.70-9.44) p<.0001	6.15 (3.16-11.96) p<.0001	21%	2.52 (1.58-4.02) p<.0001	2.09 (1.47-2.96) p<.0001	53%	1.32 (0.73-2.38) p=0.2	1.33 (0.78-2.26) p=0.17
7	Monosomy 7‡	58%	6.37 (4.46-9.11) p<.0001	7.63 (5.18-11.24) p<.0001	8%	5.57 (4.20-7.38) P<.0001	3.03 (2.50-3.67) p<.0001	70%	4.38 (2.92-6.55) p<.0001	2.60 (1.98-3.42) p<.0001

	Abnormality of 7q‡									
	del(7q)	77%	2.64 (1.54-4.52) p<.0001	2.76 (1.56-4.89) p<.0001	26%	1.66 (1.20-2.31) p=0.0002	1.51 (1.14-1.98) p<.0001	57%	1.32 (0.88-1.98) p=0.08	1.26 (0.87-1.81) p=0.11
	add(7q)	68%	4.17 (2.09-8.30) p<.0001	5.08 (2.43-10.61) p<.0001	30%	2.25 (1.34-3.79) p=0.0003	1.97 (1.33-2.94) p<.0001	33%	0.96 (0.50-1.85)p=0.9	1.01 (0.52-1.98) p=1.0
	Abnormality of 7p†	65%	4.69 (2.50-8.79) p<.0001	6.06 (3.09-11.92) p<.0001	22%	2.18 (1.39-3.43) p<.0001	1.97 (1.39-2.80) p<.0001	61%	1.30 (0.75-2.25) p=0.2	1.31 (0.79-2.17) p=0.17
8	Trisomy 8‡	80%	2.20 (1.58-3.07) p<.0001	2.64 (1.85-3.77) p<.0001	37%	1.21 (1.01-1.44) p=0.006	1.32 (1.12-1.57) p<.0001	46%	0.99 (0.80-1.23) p=0.9	1.08 (0.87-1.35) p=0.3
	t(8;21)(q22;q22) and variants‡	97%	0.26 (0.12-0.56) p<.0001	0.36 (0.16-0.81) p=0.0008	61%	.58 (0.49-0.70) p<.0001	0.60 (0.47-0.75) p<.0001	27%	0.54 (0.44-0.67) p<.0001	0.51 (0.39-0.68) p<.0001
	Abnormality of 8p11~12‡	91%	0.83 (0.12-5.62) 0.8	1.32 (0.19-9.26) p=0.7	50%	0.91 (0.43-1.92) p=0.8	1.22 (0.56-2.68) p=0.5	49%	1.08 (0.46-2.53) p=0.8	1.31 (0.57-2.98) p=0.4
9	Monosomy 9	68%	4.10 (1.34-12.53) p=0.001	5.01 (1.57-15.99) p<.0001	8%	4.04 (1.69-9.67) p=0.0004	2.55 (1.42-4.57) p<.0001	63%	3.00 (0.92-9.78) p=0.03	2.13 (0.89-5.06) p=0.02
	t(9;22)(q34;q11) and variants‡	72%	3.43 (1.45-8.12) p=0.0002	2.80 (1.08-7.27) p=0.004	14%	2.83 (1.53-5.23) p=0.0001	1.91 (1.22-3.00) p=0.0002	65%	3.95 (1.59-9.83) p=0.0008	2.32 (1.27-4.23) p=0.0002
	Deletion of 9q, including add(9q)‡	86%	1.39 (0.71-2.73) p=0.2	1.82 (0.90-3.68) p=0.03	47%	0.80 (0.58-1.09) p=0.05	0.83 (0.58-1.19) p=0.19	35%	0.66 (0.46-0.94) p=0.001	0.60 (0.38-0.96) p=0.005
11	Trisomy 11‡	75%	2.86 (1.44-5.67) p<.0001	3.25 (1.57-6.71) p<.0001	13%	2.26 (1.44-3.55) p<.0001	1.84 (1.30-2.61) p<.0001	71%	2.71 (1.52-4.84) p=.0001	2.01 (1.31-3.08) p<.0001
	All 11q23‡									
	t(9;11)(p21~22;q23) ‡	84%	1.71 (0.69-4.23) p=0.13	2.13 (0.82-5.51) p=0.03	39%	1.24 (0.75-2.04) p=0.3	1.36 (0.86-2.17) p=0.08	44%	1.00 (0.56-1.79) p=1.0	1.04 (0.57-1.89) p=0.9
	t(10;11)(p11~14;q13~23) ‡	85%	1.50 (0.43-5.29) p=0.4	2.58 (0.70-9.53) p=0.05	12%	3.57 (1.71-7.45) p=0.0001	3.29 (1.99-5.45) p<.0001	71%	4.94 (1.95-12.55) p=0.0002	3.39 (1.87-6.15) p<.0001
	t(6;11)(q27;q23)‡	96%	0.40 (0.03-5.54) p=0.4	0.63 (0.04-9.04) p=0.6	9%	2.80 (1.23-6.38) p=0.004	2.56 (1.42-4.61) p<.0001	76%	5.10 (1.79-14.52) p=0.0007	2.97 (1.53-5.74) p<.0001
	t(11;19)(q23;p13)‡	97%	0.30 (0.02-4.15) p=0.2	0.45 (0.03-6.36) p=0.4	49%	0.89 (0.46-1.71) p=0.7	1.11 (0.55-2.22) p=0.7	44%	1.03 (0.48-2.19) p=0.9	1.21 (0.57-2.56) p=0.5
	other 11q23	75%	3.03 (1.41-6.53) p=0.0002	3.87 (1.70-8.82) p<.0001	21%	2.55 (1.52-4.27) p<.0001	2.07 (1.41-3.04) p<.0001	65%	2.40 (1.26-4.59) p=0.002	1.84 (1.12-3.03) p=0.001
	Abnormality of 11q (not 11q23)†	69%	3.92 (2.27-6.76) p<.0001	4.86 (2.72-8.68) p<.0001	20%	2.33 (1.59-3.42) p<.0001	2.13 (1.59-2.86) p<.0001	62%	2.02 (1.23-3.32) p=0.0007	1.90 (1.28-2.82) p<.0001
	Abnormality 11p13~15‡	73%	3.23 (1.23-8.50) p=0.002	4.58 (1.66-12.64) p<.0001	26%	1.61 (0.86-3.01) p=0.06	1.48 (0.87-2.52) p=0.06	53%	1.08 (0.51-2.27) p=0.8	1.02 (0.48-2.15) p=1.0
12	Abnormality of 12p†									

	Monosomy 12	59%	6.07 (2.95-12.48) p<.0001	6.54 (3.05-14.00) p<.0001	6%	11.79 (5.98-23.28) p<.0001	3.67 (2.51-5.37) p<.0001	84%	21.17 (7.65-58.60) p<.0001	4.48 (2.65-7.58) p<.0001
	Other abnormality of 12p13	63%	5.06 (2.31-11.06) p<.0001	6.00 (2.62-13.73) p<.0001	14%	4.18 (2.21-7.90) p<.0001	2.58 (1.69-3.92) p<.0001	48%	1.44 (0.64-3.22) p=0.3	1.31 (0.64-2.69) p=0.3
	Other abnormality of 12p, not 12p13	57%	6.57 (3.73-11.58) p<.0001	8.45 (4.57-15.62) p<.0001	17%	4.12 (2.56-6.65) p<.0001	2.75 (1.98-3.82) p<.0001	53%	1.78 (0.94-3.37) p=0.03	1.61 (0.93-2.80) p=0.02
13	Trisomy 13[†]	70%	3.75 (2.05-6.89) p<.0001	3.62 (1.90-6.90) p<.0001	9%	2.54 (1.64-3.93) p<.0001	1.86 (1.34-2.57) p<.0001	72%	1.82 (1.05-3.14) p=0.009	1.56 (1.00-2.42) p=0.008
	Abnormality of 13q[†]									
	Monosomy 13	60%	5.87 (3.09-11.16) p<.0001	7.07 (3.57-14.02) p<.0001	8%	9.02 (5.06-16.07) p<.0001	3.48 (2.48-4.88) p<.0001	67%	5.88 (2.65-13.06) p<.0001	2.90 (1.76-4.75) p<.0001
	Deletion of 13q	85%	1.51 (0.37-6.18) p=0.4	2.10 (0.49-9.02) p=0.18	31%	1.25 (0.64-2.46) p=0.4	1.46 (0.78-2.75) p=0.12	61%	1.45 (0.65-3.26) p=0.2	1.61 (0.80-3.24) p=0.07
15	t(15;17)(q22;q21) and variants[‡]	93%	0.67 (0.43-1.04) p=0.02	1.11 (0.69-1.76) p=0.6	81%	0.40 (0.34-0.47) p<.0001	0.30 (0.23-0.39) p<.0001	13%	0.34 (0.29-0.41) p<.0001	0.19 (0.13-0.27) p<.0001
	Abnormality of 15q, not t(15;17) [†]	78%	2.53 (0.94-6.81) p=0.02	3.36 (1.15-9.83) p=0.002	46%	0.96 (0.53-1.72) p=0.9	1.10 (0.60-2.03) p=0.7	45%	0.91 (0.44-1.85) p=0.8	1.07 (0.50-2.25) p=0.8
16	inv(16)(p13q22)/t(16;16)(p13;q22)[‡]	92%	0.81 (0.46-1.44) p=0.3	0.88 (0.48-1.62) p=0.6	55%	0.66 (0.53-0.82) p<.0001	0.64 (0.49-0.84) p<.0001	46%	0.86 (0.67-1.10) p=0.10	0.85 (0.65-1.12) p=0.12
	Abnormality of 16q, not inv(16)	78%	2.45 (1.25-4.82) p<.0001	2.85 (1.41-5.79) p<.0001	31%	1.66 (1.10-2.51) p=0.003	1.60 (1.13-2.26) p=0.0004	58%	1.44 (0.87-2.40) p=0.07	1.36 (0.87-2.13)p=0.08
17	Monosomy 17	56%	6.76 (4.07-11.21) p<.0001	8.20 (4.78-14.09) p<.0001	3%	15.22 (9.37-24.72) p<.0001	3.96 (3.02-5.19) p<.0001	80%	13.68 (6.68-28.01) p<.0001	3.62 (2.43-5.41) p<.0001
	Abnormality of 17p	68%	4.08 (2.47-6.73) p<.0001	4.91 (2.86-8.41) p<.0001	25%	2.50 (1.75-3.59) p<.0001	2.11 (1.60-2.78) p<.0001	56%	1.84 (1.16-2.92) p=0.002	1.75 (1.20-2.56) p=0.0001
18	Monosomy 18	61%	5.46 (3.10-9.63) p<.0001	6.04 (3.29-11.06) p<.0001	4%	12.40 (7.28-21.11) p<.0001	3.57 (2.64-4.84) p<.0001	78%	15.76 (7.21-34.42) p<0.0001	3.61 (2.35-5.56) p<.0001
19	Trisomy 19[†]	81%	2.04 (0.85-4.91) p=0.04	2.28 (0.91-5.70) p=0.02	12%	3.11 (1.81-5.34) p<.0001	2.35 (1.61-3.42) p<.0001	74%	3.97 (2.00-7.86) p<.0001	2.54 (1.62-3.99)p<.0001
20	Monosomy 20	67%	4.35 (1.99-9.54) p<.0001	4.96 (2.19-11.21) p<.0001	6%	6.65 (3.43-12.89) p<.0001	2.98 (1.99-4.45) p<.0001	88%	8.77 (3.68-20.89) p<.0001	3.10 (1.88-5.14) p<.0001
	Abnormality of 20q	66%	4.49 (2.00-10.12) p<.0001	4.93 (2.05-11.86) p<.0001	16%	3.59 (1.86-6.94) p<.0001	2.59 (1.65-4.06) p<.0001	71%	3.81 (1.54-9.42) p=0.001	2.62 (1.44-4.77) p<.0001
21	Trisomy 21 (acquired)[‡]	74%	3.01 (1.79-5.07) p<.0001	3.36 (1.92-5.88) p<.0001	21%	1.88 (1.35-2.62) p<.0001	1.69 (1.28-2.21) p<.0001	66%	1.94 (1.28-2.96) p=0.0002	1.69 (1.20-2.37) p<.0001
	Abnormality of 21q, not t(8;21)[†]	71%	3.59 (1.80-7.15) p<.0001	4.10 (1.98-8.50) p<.0001	17%	2.37 (1.44-3.88) p<.0001	1.93 (1.34-2.80) p<.0001	61%	1.89 (0.99-3.57) p=0.02	1.66 (1.00-2.75) p=0.009
22	Trisomy 22[‡]	84%	1.67 (0.84-3.31) p=0.05	2.04 (1.00-4.14) p=0.009	47%	0.85 (0.61-1.19) p=0.2	0.90 (0.63-1.30) p=0.5	42%	0.81 (0.55-1.20) p=0.16	0.81 (0.52-1.26) p=0.2

X	Loss of X‡	87%	1.28 (0.60-2.74) p=0.4	1.89 (0.86-4.15) p=0.03	56%	0.70 (0.51-0.97) p=0.003	0.75 (0.50-1.12) p=0.06	23%	0.54 (0.37-0.78) p<.0001	0.44 (0.24-0.79) p=0.0002
Y	Loss of Y‡	89%	1.08 (0.59-1.99) p=0.7	1.47 (0.79-2.74) p=0.11	51%	0.75 (0.58-0.96) p=0.002	0.79 (0.59-1.06) p=0.04	33%	0.65 (0.48-0.86) p<.0001	0.62 (0.42-0.90) p=0.0008
Level of Karyotype Complexity	1 Abnormality	87%	per abnormality: OR 1.37 (1.30-1.46) p<.0001	per abnormality: OR 1.42 (1.33-1.51) p<.0001	47%	per abnormality HR 1.17 (1.13-1.20) p<.0001	per abnormality: HR 1.19 (1.15-1.22) p<.0001	42%	per abnormality: HR 1.09 (1.04-1.13) p<.0001	per abnormality HR 1.11 (1.06-1.16) p<.0001
Complexity	2 Abnormalities	85%			45%			40%		
	3 Abnormalities	83%			48%			35%		
	4 Abnormalities	74%			30%			51%		
	5 or More Abnormalities	62%			10%			69%		

All odds ratios/hazard ratios are given compared to Normal Karyotype.

‖Remission rates include CR with incomplete count recovery (CRi)

Method of analysis: * - logistic regression; † logrank test except for complexity (Cox regression); ‡ Cox regression

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, Odd's ratio.

Table 3: Cytogenetic entities predicting significantly poorer overall survival in multivariable analysis

Factor	HR	99% CI	p-value to enter model
Individual abnormalities			
Age (per year)	1.018	1.013-1.023	In all models
WBC (per unit increase)	1.003	1.002-1.003	
Secondary disease	1.54	1.31-1.82	
Performance status	1.15	1.09-1.21	
-5	1.82	1.34-2.48	<.0001
del(5q)/add(5q)	1.73	1.37-2.19	<.0001
inv(3)	2.52	1.76-3.62	<.0001
abn(3q)	1.85	1.38-2.48	<.0001
-7	1.51	1.22-1.88	<.0001
t(10;11)	2.62	1.59-4.29	<.0001
+8	1.33	1.12-1.57	<.0001
abn(17p)	1.63	1.21-2.20	<.0001
-17	1.58	1.15-2.17	<.0001
t(6;11)	2.25	1.26-4.03	0.0004
add(7q)/del(7q)	1.34	1.05-1.72	0.003
t(11q23)*	1.55	1.06-2.28	0.003
t(9;22)	1.64	1.04-2.56	0.004
Additional effect of complexity in above model			
>3 abnormalities	1.58	1.29-1.93	<.0001

Table 4: Revised MRC prognostic classification based on multivariable analyses

	Cytogenetic Abnormality	Comments
Favorable	t(15;17)(q22;q21) t(8;21)(q22;q22) inv(16)(p13q22)/t(16;16)(p13;q22)	Irrespective of additional cytogenetic abnormalities
Intermediate	Entities not classified as favorable or adverse	
Adverse	abn(3q) [excluding t(3;5)(q21~25;q31~35)], inv(3)(q21q26)/t(3;3)(q21;q26), add(5q), del(5q), -5, -7, add(7q)/del(7q), t(6;11)(q27;q23), t(10;11)(p11~13;q23), t(11q23) [excluding t(9;11)(p21~22;q23) & t(11;19)(q23;p13)] t(9;22)(q34;q11), -17/abn(17p), Complex (≥4 unrelated abnormalities)	Excluding cases with favorable karyotype

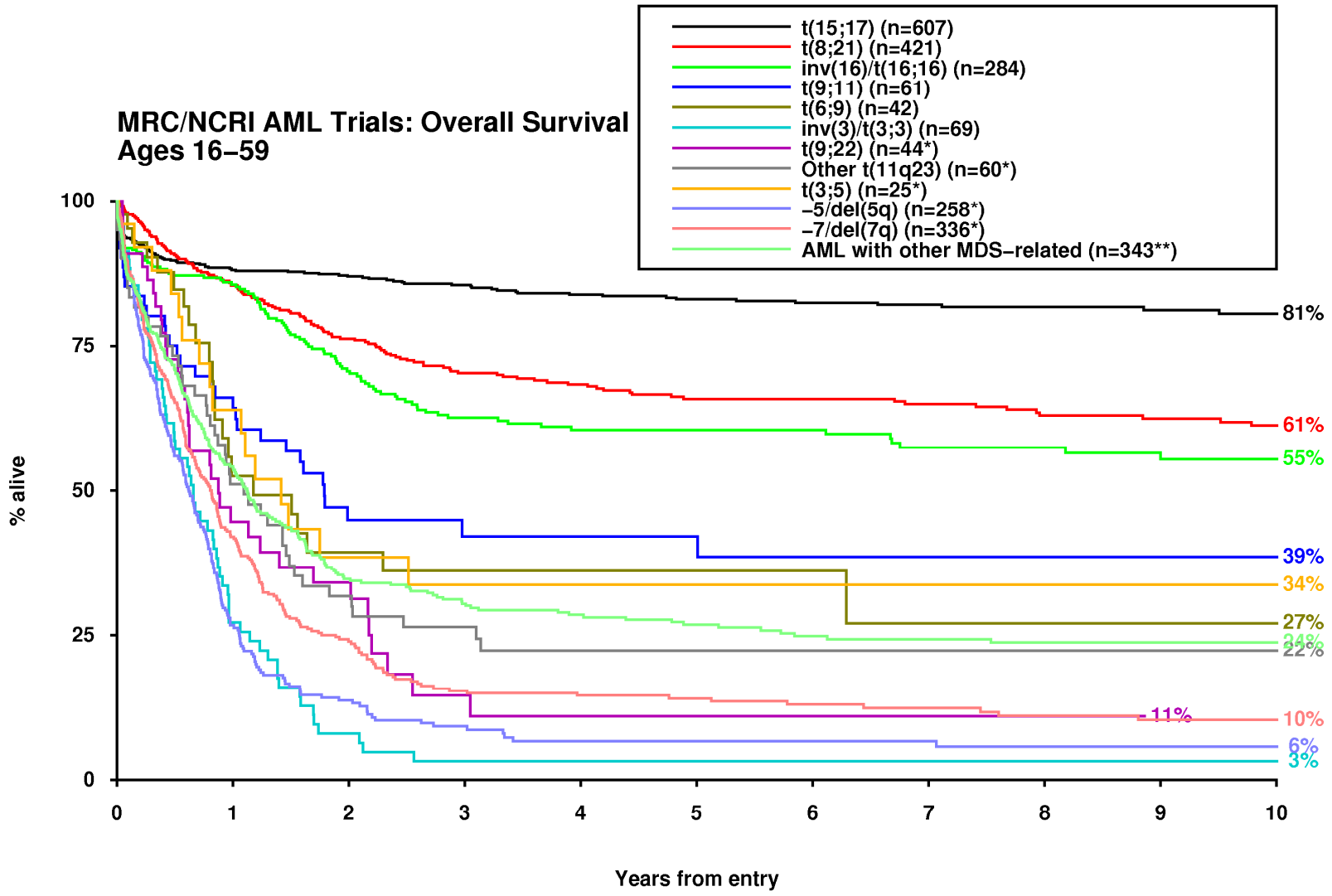
MRC/NCRI AML Trials: Overall Survival
Ages 16–59
t(15;17) (n=607)
t(8;21) (n=421)
inv(16)/t(16;16) (n=284)
t(9;11) (n=61)
t(6;9) (n=42)
inv(3)/t(3;3) (n=69)
t(9;22) (n=44*)
Other t(11q23) (n=60*)
t(3;5) (n=25*)
–5/del(5q) (n=258*)
–7/del(7q) (n=336*)
AML with other MDS–related (n=343**)
% alive
100
75
50
25
0
0
1
2
3
4
5
6
7
8
9
10
Years from entry
81%
61%
55%
39%
34%
27%
24%
22%
11%
10%
6%
3%

Figure 1

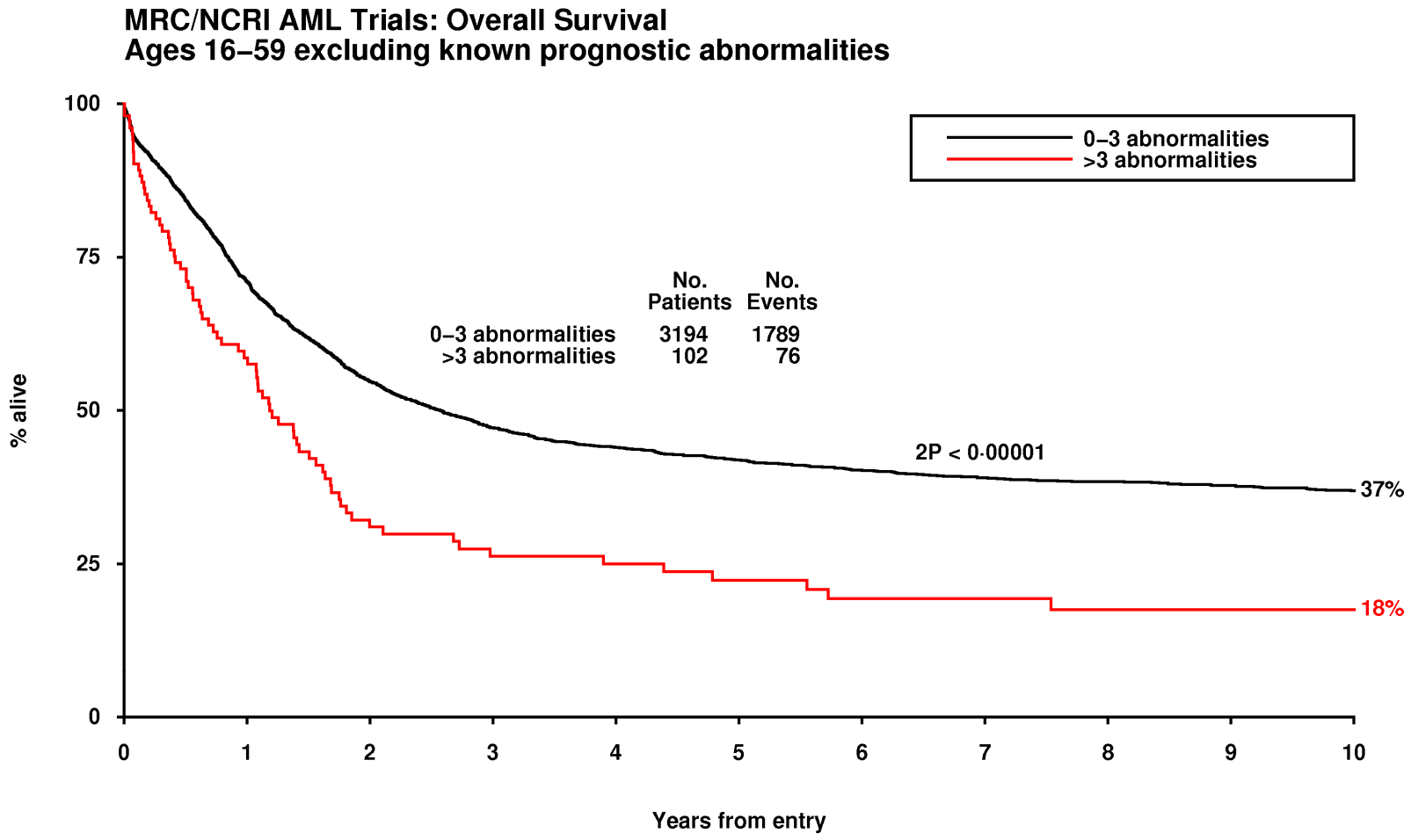
MRC/NCRI AML Trials: Overall Survival
Ages 16–59 excluding known prognostic abnormalities
0–3 abnormalities
>3 abnormalities
No. Patients
No. Events
0–3 abnormalities 3194 1789
>3 abnormalities 102 76
2P < 0·00001
37%
18%
% alive
100
75
50
25
0
0
1
2
3
4
5
6
7
8
9
10
Years from entry

Figure 2

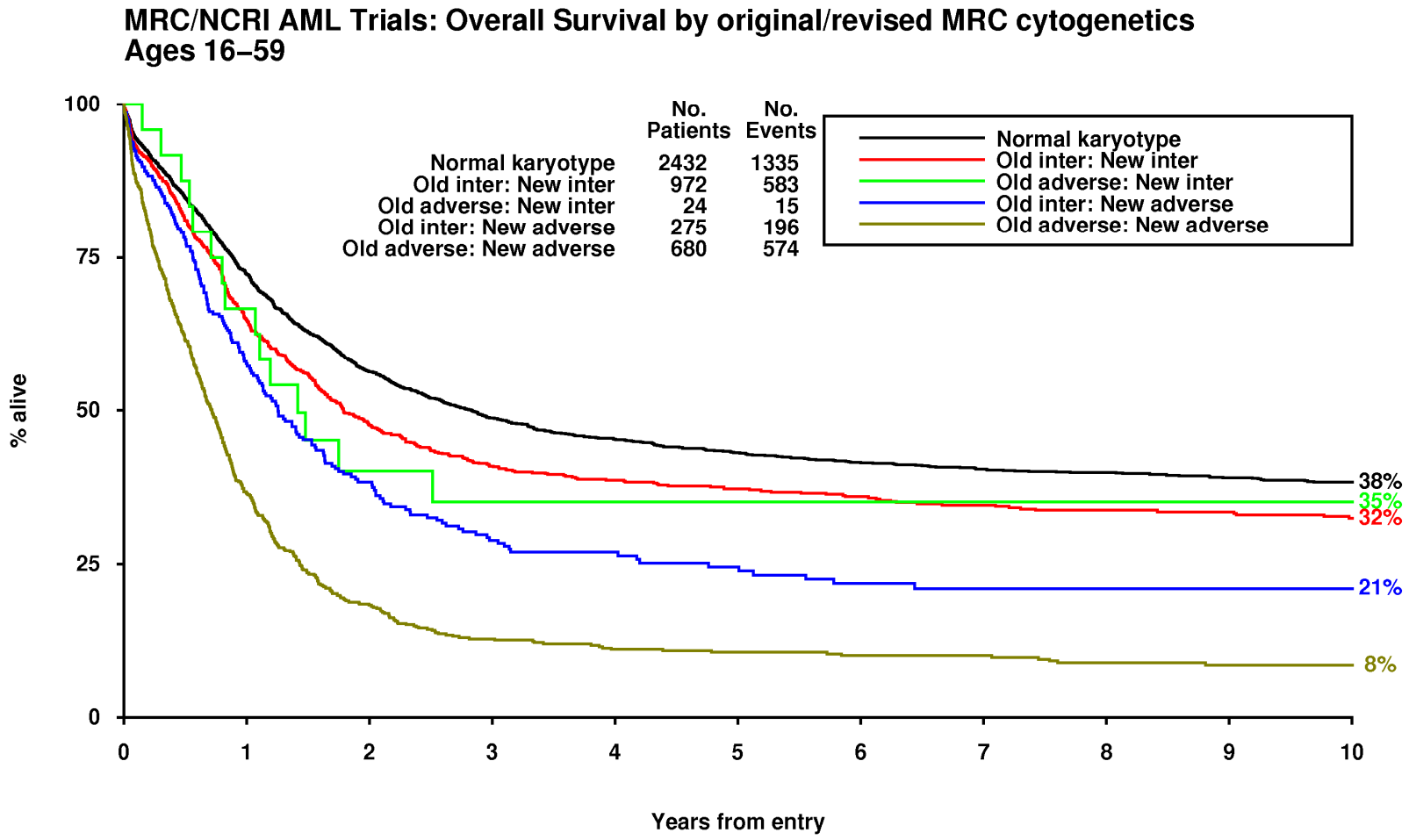
MRC/NCRI AML Trials: Overall Survival by original/revised MRC cytogenetics
Ages 16–59
No. Patients
No. Events
Normal karyotype 2432 1335
Old inter: New inter 972 583
Old adverse: New inter 24 15
Old inter: New adverse 275 196
Old adverse: New adverse 680 574
Normal karyotype
Old inter: New inter
Old adverse: New inter
Old inter: New adverse
Old adverse: New adverse
% alive
100
75
50
25
0
0
1
2
3
4
5
6
7
8
9
10
Years from entry
38%
35%
32%
21%
8%

Figure 3

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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

David Grimwade, Robert K. Hills, Anthony V. Moorman, Helen Walker, Stephen Chatters, Anthony H. Goldstone, Keith Wheatley, Christine J. Harrison and Alan K. Burnett

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