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## Factors Influencing Survival After Relapse From Acute Lymphoblastic Leukemia: A Children's Oncology Group Study

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### Abstract

Despite great progress in curing childhood acute lymphoblastic leukemia, survival after relapse remains poor. We analyzed survival following relapse among 9,585 pediatric patients enrolled on Children's Oncology Group clinical trials between 1988-2002. A total of 1961 patients (20.5%) experienced relapse at any site. The primary endpoint was survival. Patients were subcategorized by site of relapse and timing of relapse from initial diagnosis. Time to relapse remains the strongest predictor of survival. Patients experiencing early relapse less than 18 months from initial diagnosis had a particularly poor outcome with a 5-year survival estimate of 21.0±1.8%. Standard risk patients who relapsed had improved survival compared to their higher risk counterparts; differences in survival for the two risk groups was most pronounced for patients relapsing after 18 months. Adjusting for both time and relapse site, multivariate analysis showed that age (10+ yrs) and presence of CNS disease at diagnosis, male gender, and T-cell disease were significant predictors of inferior post-relapse survival. Of note, there was no difference in survival rates for relapsed patients in earlier

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versus later era trials. New therapeutic strategies are urgently needed for children with relapsed ALL and efforts should focus on discovering the biological pathways that mediate drug resistance.

## Keywords

relapsed acute lymphoblastic leukemia; Children's Oncology Group; pediatric

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## Introduction

Overall cure rates for newly diagnosed children with acute lymphoblastic leukemia (ALL) approach 80% (1,2) with currently available therapies. However, even with risk-stratified and more intensive frontline therapy, 20-25% of children with ALL still relapse, accounting for a large number of pediatric cancer patients(3-6). The treatment of patients with relapsed ALL remains unsatisfactory, with suboptimal re-induction remission rates and poor long-term overall survival rates ranging from 15-50% (7-11).

Previous studies have demonstrated that successful treatment of relapsed ALL has been closely correlated to the length of the first clinical remission (CR1) and the site of relapse (7,12). Survival after a bone marrow (BM) relapse is worse than after an extramedullary (EM) event, and the worst outcomes are significantly associated with earlier relapse while on therapy. Most papers define early relapses occurring in the first 18 months from diagnosis, intermediate relapses occurring between 18-36 months from diagnosis, and late relapses occurring after 36 months. Survival for patients experiencing early BM relapse range from 0%-15% (13,14), while those with intermediate medullary relapses have survival rates from 10-40% (12,14). For patients with late BM relapses, survival rates range from 14-50% (15). Relapses involving sites other than bone marrow have better prognoses: the survival rates for CNS relapses approach 51% (16) and those for isolated testicular relapses range from 53-84% (17,18).

Treatment for re-induction of relapsed ALL primarily involves many of the same traditional chemotherapy agents initially used as well as stem cell transplantation (SCT). The benefits of SCT versus aggressive chemotherapy for different patient groups remain unclear but the overall poor outcomes and long-term sequelae from both strategies renders neither of them ideal treatments (15,19-22). Efforts must focus on improving our understanding of the biological factors contributing to relapse and identifying new agents that will increase the chances of a sustained second remission. We conducted this retrospective study in order to determine if patterns of survival after relapse have changed with more intensive frontline therapy on contemporary clinical trials. We describe the diagnostic characteristics and outcomes after relapse for a large number of patients relapsing on the generation of COG trials opened from 1988-2002, in order to determine if newer treatment strategies have altered the survival of ALL following relapse.

## Materials and Methods

### Clinical trials

Data used in this study were collected as part of Children's Cancer Group (CCG) protocols that enrolled patients between December 1988 and 2002. All patients and guardians participated on these trials with informed consent. A total of 9,585 children with newly diagnosed B-precursor or T-cell ALL were enrolled in CCG-1881, CCG-1882, CCG-1883, CCG-1891, CCG-1901, CCG-1922, CCG-1952, CCG-1953, CCG-1961, and CCG-1962 trials. For all protocols, any patient with a diagnosis of mature B-cell leukemia or AML was ineligible for enrollment. A description of these trials, accrual dates, total enrollment, and overall 5- year event-free survival (EFS) rates are listed in Table 1. Table 2 compares the clinical

characteristics of the patients who relapsed with those who remained in CR1. The primary endpoint was overall survival after first relapse (information on subsequent adverse events was not collected). Following relapse on initial trials, the only data collected was survival. Thus, we cannot comment on event-free survival or analyze outcome based on the treatment administered post relapse.

### Risk stratification

The risk stratification algorithms used for patient eligibility are summarized below. For studies open prior to 1995: Low risk: 2 to 9 years of age at diagnosis with an initial WBC count less than 10,000/ $\mu\text{L}$  (23). Intermediate risk: ages 2 to 10 years with a WBC 10,000 to 50,000/ $\text{mm}^3$ , no bulky extramedullary disease, or, in boys with platelet counts less than 100,000/ $\text{mm}^3$ , a WBC less than 10,000/ $\text{mm}^3$ , or in children 1 to 2 years of age, a WBC less than 50,000/ $\text{mm}^3$ (24). High risk: 1 to 9 years old with  $\text{WBC} \geq 50 \times 10^9/\text{L}$  or  $\geq 10$  years old irrespective of WBC, excluding patients with lymphomatous features(21).

For studies including CCG 1922, 1952, 1953, 1961, and 1962, risk stratification followed the NCI-Rome risk criteria (25): Standard risk: Age 1 through 9.99 years and diagnostic WBC  $< 50,000 \mu\text{L}$ . High risk: all others up to the age of 21 years.

Immunophenotypic classification was determined as follows: B lineage ALL:  $>30\%$  CD19 positivity,  $\pm >30\%$  CD10 or CD 20 positivity; T lineage ALL:  $>30\%$  CD7 positivity. Diagnostic karyotyping of leukemic cells was performed by local institutions prior to the initiation of therapy; however results were not uniformly submitted for central review.

### Statistical analyses

Differences in proportions of clinical characteristics at diagnosis between patients who relapsed and those who did not, were assessed using chi-square tests. Outcome analyses used life table methods and associated statistics. The primary endpoint examined was overall survival post relapse. Life table estimates were calculated by the Kaplan-Meier (KM) procedure(26) and the standard error (SE) of the life table estimate was obtained by the method of Peto(27). The log rank test was used to compare outcome between groups. Cox proportional hazards regression models were used to evaluate the significance of differences in survival between groups. When the proportional hazards assumption seemed unsatisfactory for a predictor in the Cox model, the effects of other variables were adjusted by stratifying the predictor in question. Five-year post-relapse survival rates are presented here for various subgroups.

## Results

### Overview of clinical trials

Between 1988 and 2002, a total of 9,585 patients with *de novo* ALL were enrolled on CCG clinical trials and 1961 children experienced a relapse at any site. The distribution of relapse sites was as follows: Isolated marrow 57.3%, Concurrent marrow 13.5%, Isolated CNS 20.9%, Isolated testicular 5.3%, Other extramedullary  $\pm$  CNS 3.1%. Overall enrollment and 5-year event-free survival (EFS) rates by protocol are given in Table 1. Event-free survival rates ranged from 37.6% to 82.3%. Among all relapsed patients, the median follow-up time from initial diagnosis was 51.6 months. After experiencing relapse, the median follow-up time was 15.7 months. Duration of CR1 for patients who relapsed varied accordingly with NCI risk group at diagnosis, with shorter duration of remission coinciding largely with higher risk features at diagnosis (Table 1 and Table 2). Of 1961 total patients who relapsed, 837 were alive at their last follow-up. Three patients died on the day of relapse. In addition, follow-up data after relapse was not available for 49 patients. For era of trial enrollment, we defined early trials to include 1881, 1882, 1883, 1891, 1901, and 1922. Later trials included 1952, 1953,

1961, and 1962. Of note, at the time of this analysis, results from CCG 1991 for standard risk ALL patients were still blinded and not available.

A comparison of diagnostic features of patients who relapsed with those who did not is given in Table 2. The relapsed cohort had a higher percent of patients who fell in the age range  $< 1$  or  $\geq 10$  years ( $p=0.0001$ ). Similarly, there was a higher proportion of males in the relapsed group ( $p=0.0002$ ). Nearly 20% of the patients who relapsed presented with an initial WBC  $>100,000/\mu\text{L}$ . In comparison to Caucasians, more children of African American or Hispanic ethnicity experienced relapse ( $p=0.0001$ ). There was no significant difference in the distribution of immunophenotype (B-precursor or T cell) between the patients who relapsed versus those who did not. It was not possible to determine the distribution of other diagnostic variables such as cytogenetics, because of insufficient data.

Measurements of early response to therapy were captured by day 7 and/or day 14 marrow morphology status, though not all studies uniformly captured both time points. Of the 4,064 patients achieving an M1 marrow by day 7, 662 (16.2%) relapsed, while 537 of 2,547 (21.1%) patients with a slower response to initial therapy (e.g. achieving an M1 marrow by day 14) experienced relapse ( $p=0.0001$ ). Of the 630 patients who were M2 or M3 on day 14, 263 (41.7%) relapsed ( $p=0.0001$ ). Taken together, this data supports the previous observation that slow early response is associated with inferior EFS.

### Features associated with survival after relapse

Relapse events were defined by time from initial diagnosis (early:  $<18$  months; intermediate: 18-36 months; late:  $\geq 36$  months) and site (isolated marrow, concurrent marrow, isolated CNS, isolated testicular, other extramedullary +/- CNS). Table 3 gives five-year survival rates following relapse by site and timing of relapse.

Overall post-relapse survival rates were higher ( $p < 0.0001$ ) for patients with isolated CNS relapse ( $58.7 \pm 3.2\%$ ) than for patients with either isolated ( $24.1 \pm 2.1\%$ ) or concurrent bone marrow ( $39.4 \pm 5.0\%$ ) relapses. Survival rates after early relapse were higher for patients with isolated CNS relapse than for patients with either isolated or combined bone marrow relapse (5 year survival rates – isolated CNS:  $43.5 \pm 4.5\%$  vs isolated marrow:  $11.5 \pm 1.9\%$  vs concurrent marrow:  $11.6 \pm 4.9\%$ ,  $p < 0.0001$ ). This was also true for intermediate and late relapsing patients. Survival rates were also significantly higher for patients with concurrent marrow relapses compared to those with isolated marrow relapses – overall ( $p < 0.0001$ ), intermediate ( $p = 0.002$ ), late ( $p = 0.02$ ). Survival rates were identical for the early relapse patients with any marrow involvement. Survival curves post relapse by timing of relapse are given in figures 1A, 1B, and 1C for isolated marrow, concurrent marrow and isolated CNS relapses, respectively. Estimates of 5-year survival rates for isolated marrow relapse in early ( $n=412$ ), intermediate ( $n=324$ ), and late ( $n=387$ ) relapsing patients were  $11.5 \pm 1.9\%$ ,  $18.4 \pm 3.1\%$ , and  $43.5 \pm 5.2\%$ , respectively (Table 3, Figure 1A,  $p < 0.0001$ ). Overall, patients with early isolated marrow relapse had a relative risk of death about 3.7-fold higher than patients with a late relapse and it was 2.3-fold higher for patients with an intermediate isolated marrow relapse patients compared to those with late relapses. Similarly, the rates for concurrent marrow relapse were  $11.6 \pm 4.5\%$  ( $n=86$ ),  $39.8 \pm 9.3\%$  ( $n=54$ ), and  $60.3 \pm 8.3\%$  ( $N=124$ ), respectively (Table 3, Figure 1B,  $p < 0.0001$ ). Relative risk of death was 4.9-fold and 2.0-fold higher for early and intermediate relapse patients respectively, compared to patients with late concurrent marrow relapse. Five-year survival rates post isolated CNS relapse were: Early ( $N=175$ ):  $43.5 \pm 4.5\%$ , Intermediate ( $N=180$ ):  $68.0 \pm 4.6\%$ , Late ( $N=54$ ):  $78.2 \pm 8.8\%$  (Table 3, Figure 1C,  $p < 0.0001$ ). The relative risk of death for patients with early and intermediate CNS relapses were 3.4-fold and 1.5-fold respectively, compared to that for patients experiencing late CNS relapses. Overall survival rates after relapse, by timing of relapse were similar for 104 patients experiencing an isolated testicular relapse; their 5-year post-relapse survival rate was  $58 \pm 8.2\%$  (data not

shown). There was no significant difference in survival rates for patients experiencing early versus intermediate versus late testicular events.

Overall, patients who were NCI SR at diagnosis had better outcomes than NCI HR patients (RHR=2.4,  $p<0.0001$ ; 5-year survival rates- NCI SR:  $50.4\pm 2.4\%$  versus NCI HR:  $22.6\pm 2.1\%$ ). There were significant differences in outcome for those SR versus HR patients experiencing either an early ( $33.1\pm 3.6\%$  vs  $14.9\pm 2.1\%$ , RHR=2.0,  $p<0.0001$ ), intermediate ( $52.2\pm 3.7\%$  vs  $22.0\pm 3.9\%$ , RHR=2.4,  $p<0.0001$ ) or late relapse ( $59.6\pm 4.6\%$  vs  $39.5\pm 7.2\%$ , RHR=2.0,  $p<0.0001$ )(Figure 2).

In general, frontline therapy for ALL has intensified over time in order to improve event-free survival. It has been speculated that patients treated intensively at initial diagnosis might be more refractory to salvage therapy. In order to examine this further, we assessed survival after relapse for patients with any marrow relapse stratified by treatment era (early vs late trials). We defined early treatment protocols to include CCG 1881, 1882, 1883, 1891, 1901, and 1922, and later era trials to include CCG 1952, 1953, 1961, and 1962. A total of 1961 children were included in this analysis (Figure 3). The results demonstrated that patients who relapsed early had dismal survival regardless of treatment era (5-year post-relapse survival:  $19.3\pm 2.1\%$  versus  $23.4\pm 3.4\%$ ,  $p=0.10$ ). Similarly, there were no statistically significant differences in survival between those treated on early vs late trials, for patients experiencing either an intermediate ( $39.3\pm 3.3\%$  versus  $36.0\pm 4.8\%$ ,  $p=0.49$ ) or late relapse ( $53.3\pm 4.3\%$  versus  $54.4\pm 9.2\%$ ,  $p=0.66$ ).

Univariate analyses ( $n=1961$ ) were conducted to study the association of presenting clinical and laboratory features at initial diagnosis, time to relapse, and site of relapse with survival post relapse (Table 4). Significant associations were found with site and timing of relapse, age at diagnosis, WBC at diagnosis, lineage (B vs T), CNS status at diagnosis, race, and NCI risk; exceptions were trial era and sex. Multivariate analyses stratified by timing of relapse and site of relapse were conducted on the subset of patients ( $n=1391$ ) with complete data for all the variables (Table 5). Infants  $< 1$  year of age at diagnosis were excluded from the multivariate analyses, since they cannot be classified by NCI risk group. Age at diagnosis, CNS disease, sex, lineage, and NCI risk group were significant predictors of survival post relapse. Trial era, WBC at diagnosis, and race were not significant in predicting survival in the multivariate analysis. Multivariate analyses stratified for time to relapse, site of relapse, and age at diagnosis resulted in the same significant predictors as before. Trial era, WBC at diagnosis, and race were not significant factors.

## Discussion

Despite improved treatments and increasing dose intensity in primary therapy for newly diagnosed patients with ALL, patients with relapsed disease continue to account for a large number of pediatric cancer patients (28). The current study analyzed survival following relapse for almost 10,000 children diagnosed with ALL between 1988-2002, of whom 1,961 (20.5%) relapsed. Not surprisingly, survival after relapse remains most dismal for those patients experiencing a bone marrow relapse within 18 months of initial diagnosis. High risk patients have higher mortality than their standard risk counterparts irrespective of the time to relapse. Male sex, age  $< 1$  year or  $\geq 10$  years at diagnosis, T-cell lineage, and CNS disease at diagnosis persist as predictors of increased risk of death after relapse, even when controlled for by site and time to relapse. New studies clearly need to address how to effectively treat relapsed patients and maintain durable remissions.

Our analysis failed to demonstrate any substantial differences in survival after relapse for patients treated on a recent generation COG sponsored ALL trial versus 762 children enrolled on earlier CCG trials between 1983-1989 (12). While we have witnessed improved EFS for

newly diagnosed patients by exposing them to more intense treatment and potentially greater morbidity, we remain unable to salvage the majority of children who fail initial therapy. The data presented here support our ongoing efforts to optimize risk stratification to identify patients at diagnosis who require more intense or novel therapies to achieve cure. In particular, this report provides compelling data that NCI HR patients do exceptionally poorly after relapsing at any time, thus warranting new approaches to optimizing therapy at diagnosis.

It is curious to note that while no differences in survival following relapse were noted for patients relapsing off older era trials versus more contemporary trials, patients who are SR at diagnosis have improved survival compared to their HR counterparts irrespective of time to relapse. Certainly, the distribution of patients experiencing early, intermediate, and late relapses were highly skewed towards NCI HR patients in the former group and NCI SR in the latter group (Figure 2b). While NCI SR patients receive less intense therapy, the data suggests that intrinsic differences in the biology of the leukemic blasts is correlated with different mechanisms and timing of relapse. For instance, NCI SR patients have a much higher incidence of favorable genotypes like hyperdiploidy and *TEL-AML1* while older patients are more likely to be *BCR-ABL* positive.

Previously, Gaynon and colleagues reported survival after ALL relapse of children enrolled on Children's Cancer Group clinical trials between 1983-1989 (12). In that analysis, the strongest predictor of prolonged survival after relapse was an initial time to first relapse  $\geq 36$  months. Importantly, patients with an isolated BM relapse who failed initial therapy less than 18 months from diagnosis had a 4.5-fold higher relative risk for death than those relapsing after 36 months. In our updated analysis and a review of the literature, the two most significant predictors of survival after relapse remain the same—site and time. This observation continues to raise essential questions about the biology of relapsed ALL which will need to be addressed if we are going to be remotely successful in curing these patients.

Indeed, recent analyses have indicated that there is a unique and distinct pattern of gene expression in pairs of relapsed samples from patients who relapse early from those who relapse later (29). It has been shown that paired samples from patients experiencing early relapse are more similar in expression patterns than paired samples from those relapsing later. Early relapse is also characterized by increased expression of genes involved in proliferation and survival (29). It is likely that resistant leukemia cells in patients destined to relapse early are present in the initial diagnostic field of blasts. Late relapse may be due to the acquisition of further somatic and/or epigenetic changes. Moreover been shown by analyzing microsatellite markers that some very late relapses of *TEL/AML1* positive leukemia likely represent a new event that occurs in a quiescent precursor leukemia cell harboring an otherwise silent fusion gene that has escaped eradication during initial therapy(30,31).

Studying the biology of these diseases, both at diagnosis, in minimal residual disease states after selection by chemotherapy, and at relapse, would ideally improve an understanding of how to use current therapy as well as identify new targets. To date, several drug combinations have achieved substantial complete response 2 (CR2) rates varying from 68 to 94% depending on the timing of relapse; however, patients who fail to enter CR2 are not likely to be salvaged with a different combination suggesting intrinsic drug resistance and a defect in terminal cell death pathways. Moreover re-induction rates for patients with multiply relapsed ALL cluster around 40%, suggesting that we have yet to truly understand and circumvent the mechanisms by which resistant lymphoblasts escape cytotoxicity(8-11,32,33).

For newly diagnosed ALL patients, the challenge that remains is to accurately identify patients who will benefit the most from intensive primary therapy. However, this analysis demonstrates that survival for patients with relapsed ALL using conventional therapy remains woefully

inadequate, particularly for those who relapse within 36 months of initial diagnosis. As a result of these and other analyses, recent efforts in the Children's Oncology Group have focused on offering uniform clinical trials for patients with relapsed ALL while gathering important biologic data, thus taking the first steps toward defining whether agents not typically used in treatment of ALL at initial diagnosis can improve outcome for relapse. The extremely poor survival following relapse underscores the need to focus on improving the outcome of primary therapy for these patients who are unlikely to be salvaged if they relapse. Promising new therapies should be rapidly integrated into trials for subsets of higher risk patients at initial diagnosis.

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Figure 1A

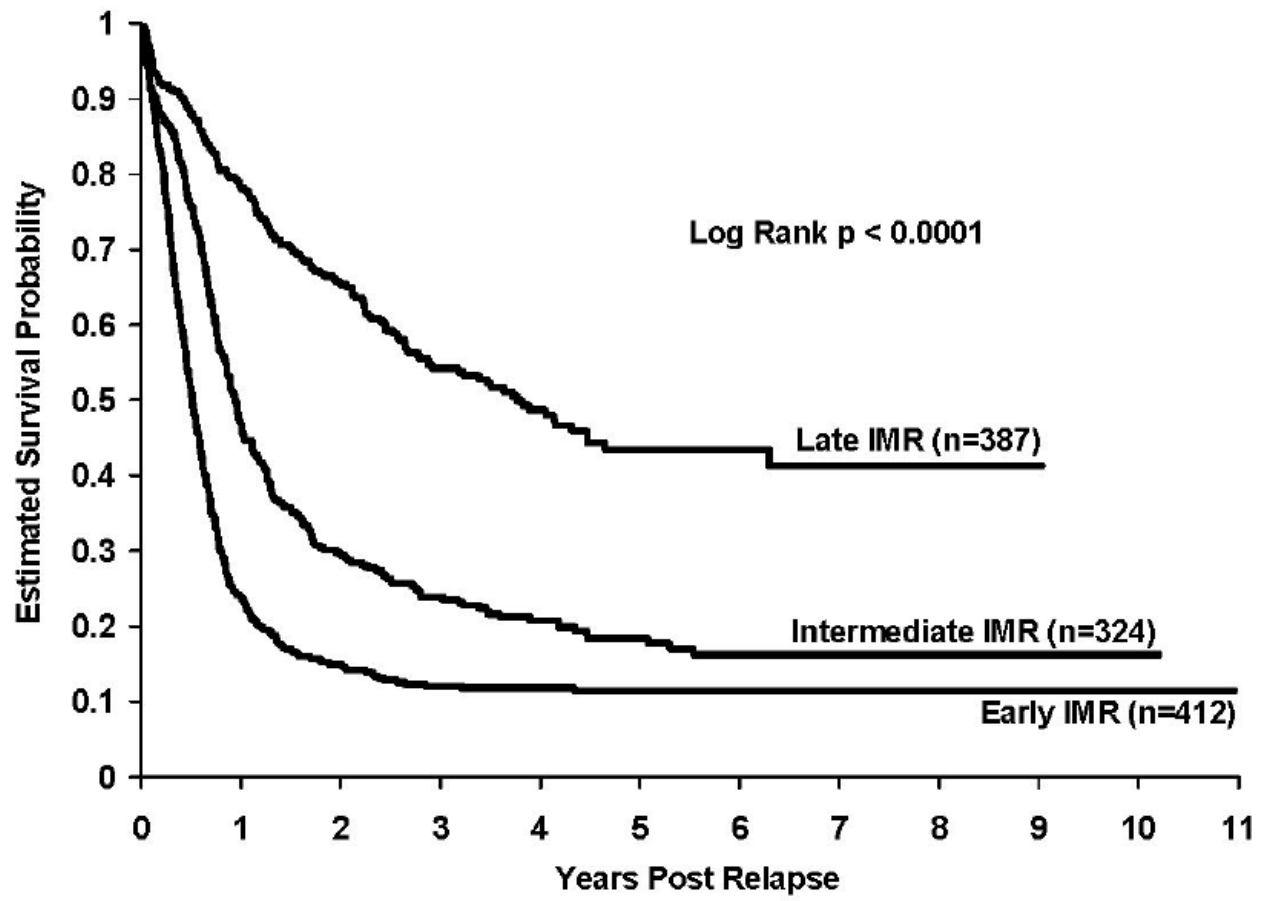


Figure 1B

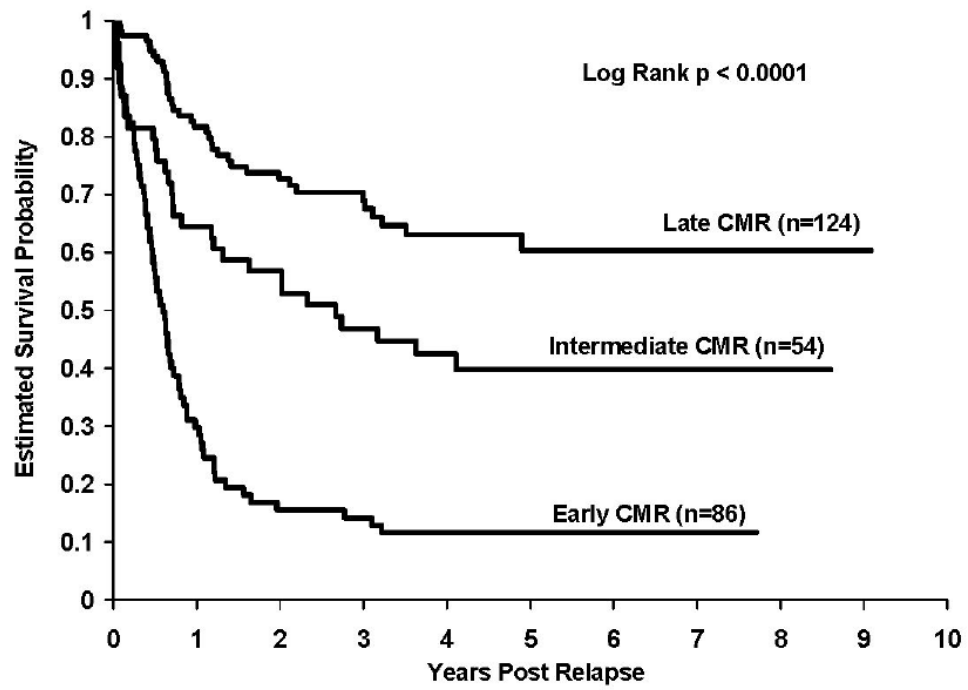
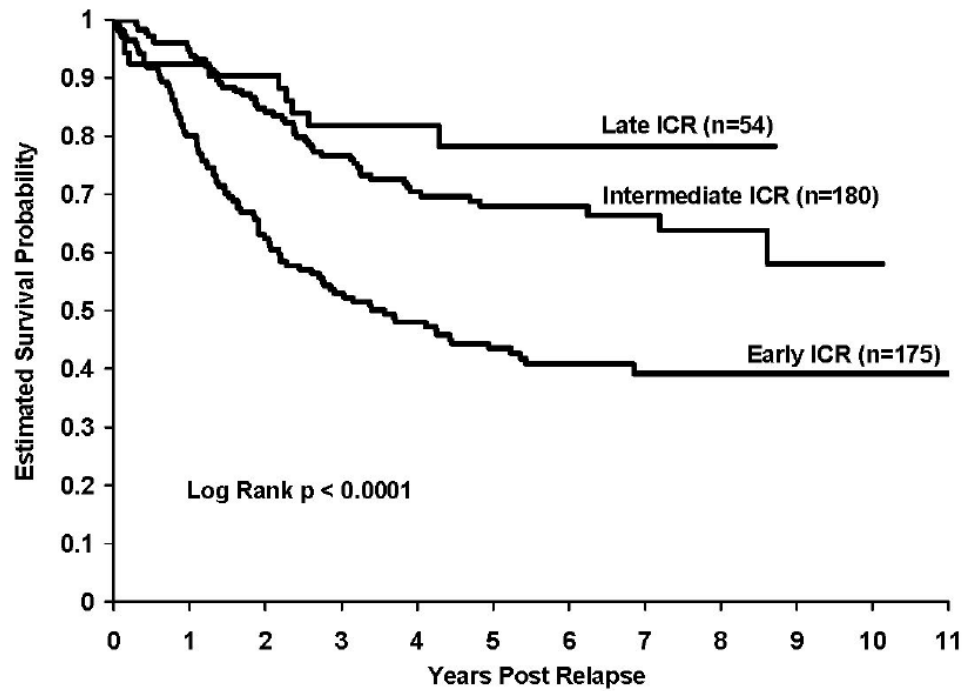


Figure 1C

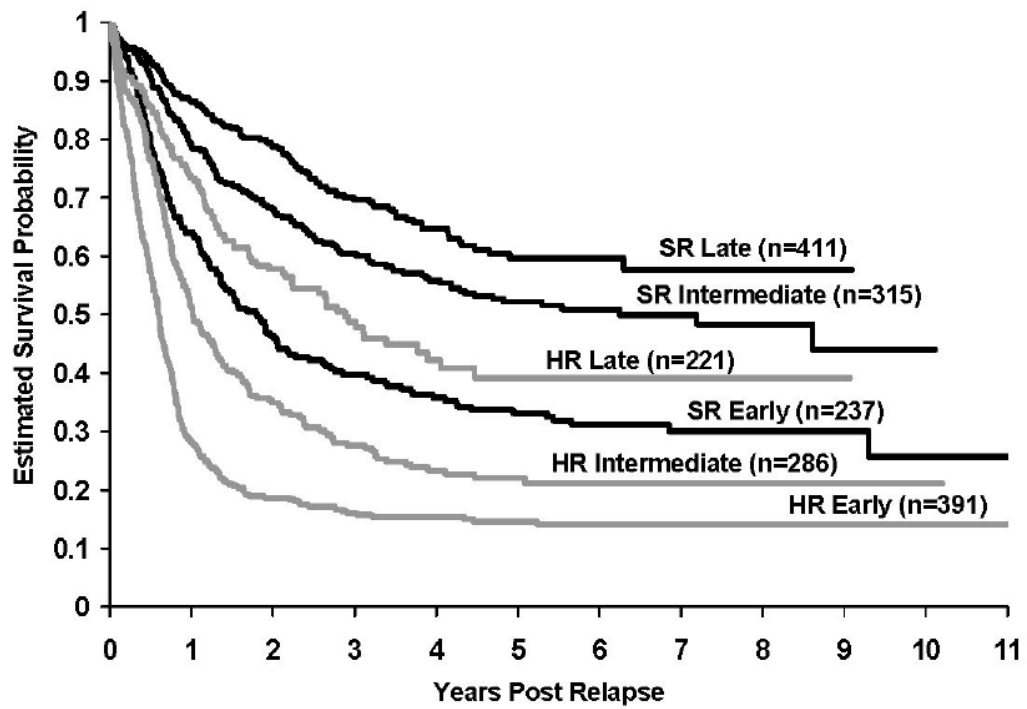


**Figure 1.**  
**Figure 1A: Survival after relapse for patients experiencing isolated marrow relapse.**  
 Survival rates at 5 years after relapse for patients with isolated marrow relapse by timing of

relapse (early: 11.5±1.9%, intermediate: 18.4±3.1%, late: 43.5±5.2%),  $p<0.0001$ . RHR: early vs late = 3.7, intermediate vs late = 2.3.

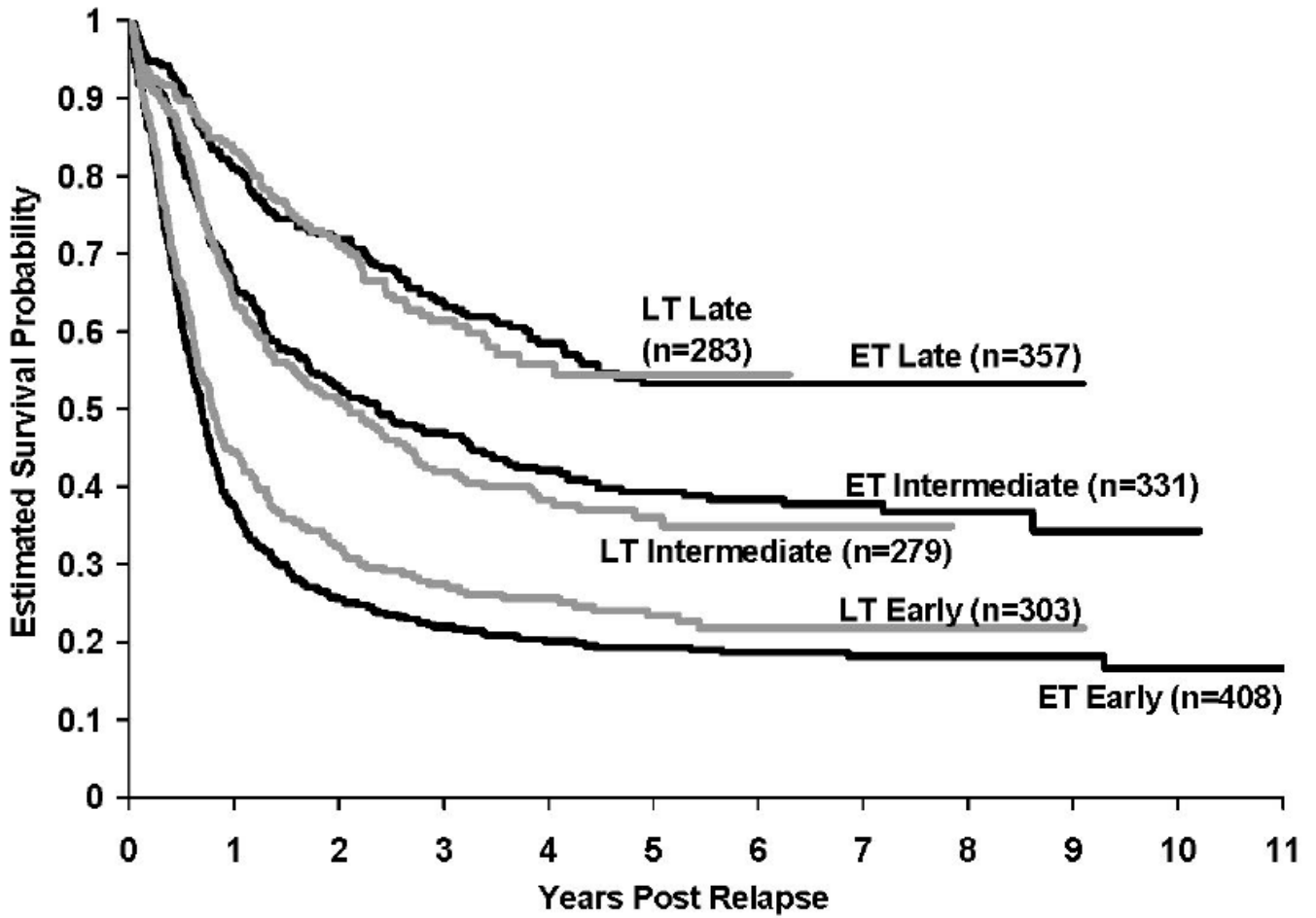
**Figure 1B: Survival after relapse for patients experiencing concurrent marrow relapse.** Survival rates at 5 years after relapse for patients with concurrent marrow relapse by timing of relapse (early: 11.6±4.5%, intermediate: 39.8±9.3%, late: 60.3±8.3%),  $p<0.0001$ . RHR: early vs late = 4.9, intermediate vs late = 2.0.

**Figure 1C: Survival after relapse for patients experiencing isolated CNS relapse.** Survival rates at 5 years after relapse for patients with isolated CNS relapse by timing of relapse (early: 43.5±4.5%, intermediate: 68.0±4.6%, late: 78.2±8.8%),  $p<0.0001$ . RHR: early vs late = 3.4, intermediate vs late = 1.5.



**Figure 2. Kaplan-Meier estimates of survival after relapse for patients stratified by NCI risk group at diagnosis and timing of relapse**

There were significant differences in outcome for those SR versus HR patients experiencing either an early ( $33.1 \pm 3.6\%$  vs  $14.9 \pm 2.1\%$ ,  $p < 0.0001$ ), intermediate ( $52.2 \pm 3.7\%$  vs  $22.0 \pm 3.9\%$ ,  $p < 0.0001$ ) or late relapse ( $59.6 \pm 4.6\%$  vs  $39.5 \pm 7.2\%$ ,  $p < 0.0001$ ).



**Figure 3. Kaplan-Meier estimates of survival after relapse for patients stratified by treatment era and timing of relapse**

There was no difference in survival between Early and Late trials among patients who experienced either an early relapse ( $19.3 \pm 2.1\%$  vs  $23.4 \pm 3.4\%$ ,  $p=0.10$ ), or intermediate relapse ( $39.3 \pm 3.3\%$  vs  $36.0 \pm 4.8\%$ ,  $p=0.49$ ), or late relapses ( $53.3 \pm 4.3\%$  vs  $54.4 \pm 9.2\%$ ,  $p=0.66$ ).

Table 1

Clinical trials sponsored by CCG during 1988-2002

Trial	Accrual dates	Risk group	Study Question	N	5- year EFS±SE <sup>1</sup>	# of Relapses (% per protocol)	Median (range) length of CR1 <sup>2</sup>	Median follow-up time <sup>3</sup>	Median follow-up time <sup>4</sup>
1881	12/88-12/92	Low	Randomization of DJ <sup>5</sup> vs. standard therapy.	778	79.9±1.5%	152 (19.5%)	36.1 (2.6, 120.9)	91.9	49.0
1882	5/89-6/95	Higher	Efficacy of post-induction intensification for higher risk patients with a slow response to initial therapy.	1525	68.3±1.3%	388 (25.4%)	23.1 (0.1, 113.4)	35.7	8.6
1883	12/88-8/93	Infant	Treatment of infants less than 12 months of age.	135	37.6±4.3%	75 (55.6%)	5.5 (0.6, 69.3)	16.6	6.6
1891	1/90-7/93	Intermediate	Efficacy of double DI vs. single DI	1204	79.6±1.2%	223 (18.5%)	28.7 (0.6, 124.8)	73.7	33.7
1901	12/90-9/94	High	Treatment of newly diagnosed children with multiple unfavorable presenting features	418	73.0±2.3%	79 (18.9%)	16.1 (1.7, 67.8)	28.9	8.7
1922	3/93-8/95	Standard	Randomized comparison IV vs. oral 6-MP and dexamethasone vs. prednisone	1061	82.3±1.3%	179 (16.9%)	30.5 (2.1, 86.7)	67.7	25.0
1952	5/96-2/00	NCI Standard	Randomized comparison of oral 6-MP vs. 6-TG and intrathecal MTX vs ITT.	2174	81.7±0.1%	371 (17.1%)	31.5 (0.5, 110.6)	69.0	26.6
1953	7/96-8/00	Infant	Treatment of infants with intensive early systemic and intrathecal therapy.	115	43.1±4.9%	24 (20.9%)	8.9 (1.1, 69.2)	14.1	4.0
1961	9/96-5/02	NCI High	Randomized comparison of standard versus augmented BFM and single versus double DI.	2057	71.5±1.3%	443 (21.5%)	21.1 (0.2, 112.2)	37.2	9.9
1962	3/97-11/98	NCI Standard	Randomized comparison of PEG-	118	78.8±4.3%	27 (22.9%)	30.2 (6.7, 93.1)	68.6	24.1

Trial	Accrual dates	Risk group	Study Question	N	5- year EFS±SE <sup>1</sup>	# of Relapses (% per protocol)	Median (range) length of CR1 <sup>2</sup>	Median follow-up time <sup>3</sup>	Median follow-up time <sup>4</sup>
			asparaginase with native E.coli asparaginase on the standard arm of the CCG-1952 trials.						
			Total	9585		1961	26.0 (0.1, 124.8)	51.6	15.7

<sup>1</sup> Standard error

<sup>2</sup> Only among relapsed ALL patients (time in months)

<sup>3</sup> Median follow-up time (time in months) for relapsed patients from initial diagnosis

<sup>4</sup> Median follow-up time (time in months) for relapsed patients from relapse diagnosis

<sup>5</sup> DI=Delayed Intensification



**Table 2**  
**Characteristics of 9585 patients enrolled on CCG trials between 1988-2002**

Features at initial diagnosis	Total number of patients	Number of patients in CCR (% of overall group)	# of relapsed patients (% in relapsed group)	5-year EFS (SE)	
<b>Gender</b>	Male	5374	4195 (55.0)	1179 (60.1)*	74.0 (0.6)@
	Female	4211	3429 (45.0)	782 (39.9)	77.6 (0.7)
<b>Age</b>	<1 year	250	151 (2.0)	99 (5.1)*	40.1 (3.2)@
	1-9.99 years	6940	5626 (73.8)	1314 (67.0)	79.2 (0.5)
	≥ 10 years	2395	1847 (24.2)	548 (27.9)	68.5 (0.1)
<b>Race</b>	White	6830	5514 (72.3)	1316 (67.1)*	77.1 (0.5)@
	Black	507	373 (4.9)	134 (6.8)	67.6 (2.4)
	Hispanic	1636	1262 (16.6)	374 (19.1)	72.5 (1.2)
	Other	612	475 (6.2)	137 (7.0)	73.6 (2.0)
<b>WBC</b>	<50K	7344	5974 (78.4)	1370 (69.9)*	78.6 (0.5)
	50-100K	1009	776 (10.2)	233 (11.9)	70.4 (1.6)
	>100K	1227	870 (11.4)	357 (18.2)	61.9 (1.6)
	Unknown	5	4	1	
<b>CNS Status</b>	CNS 1	8359	6743 (90.3)	1616 (84.3)*	77.1 (0.5)
	CNS 2	706	514 (6.9)	192 (10.0)	66.3 (1.9)
	CNS 3	317	208 (2.8)	109 (5.7)	58.1 (3.0)
	Unknown	203	159	44	
<b>Testicular disease</b>	Normal	5173	4040 (98.2)	1133 (97.8)	74.2 (0.7)
	Enlarged	101	76 (1.8)	25 (2.2)	65.0 (5.1)
	Unknown/NA	4311	3508	803	
<b>Immunophenotype</b>	B-lineage	5754	4470 (85.6)	1284 (86.5)	75.2 (0.6)
	T-lineage	953	752 (14.4)	201 (13.5)	73.0 (1.6)
	Other/unknown	2878	2402	476	

\* p-value < 0.001 (Significant difference in clinical characteristic between relapsed vs. did not relapse)

@ p-value < 0.001 (Significant differences in EFS between categories for the clinical characteristic)

**Table 3**  
**Overall five-year survival (OS) rates after relapse, by site and time to relapse**

5-year Survival Post Relapse	Relapse Site														
	Isolated Marrow Relapse			Concurrent Marrow Relapse			Isolated CNS Relapse			Isolated Testicular Relapse			Other extramedullary +/- CNS Relapse		
	n	Survival (%)	SE	n	Survival (%)	SE	n	Survival (%)	SE	n	Survival (%)	SE	n	Survival (%)	SE
<b>Time to relapse</b>															
<b>Early<sup>1</sup></b>	412	11.49	1.91	86	11.64	4.89	175	43.51	4.45	15	13.64	16.56	23	10.38	11.32
<b>Intermediate<sup>1</sup></b>	324	18.42	3.09	54	39.79	9.31	180	67.99	4.53	35	52.20	11.41	17	50.47	25.12
<b>Late<sup>1</sup></b>	387	43.46	5.23	124	60.34	8.29	54	78.25	8.85	54	59.96	15.49	21	85.15	14.67
<b>Overall<sup>2</sup></b>	1123	24.1	2.1	264	39.4	5.0	409	58.7	3.2	104	58.0	8.2	61	55.9	9.9

<sup>1</sup> p-value < 0.0001 compares survival rates by sites of relapse within each time period.

<sup>2</sup> "Overall survival" refers to an unadjusted comparison of sites of relapse.

**Table 4**  
**Univariate analyses of risk factors associated with survival after relapse**

Univariate Analyses of Survival Post Relapse risk Factors (N=1961)		5-year Survival rates post relapse ± SE (%)	p-value
<b>Time to relapse</b>	Early	21.0±1.8	<0.0001
	Intermediate	37.9±2.7	
	Late	53.1±3.9	
<b>Relapse Site</b>	Isolated marrow	24.1±2.1	<0.0001
	Concurrent marrow	39.4±5.0	
	Isolated CNS	58.7±3.2	
	Isolated testicular	58.0±8.2	
	Other extramed ± CNS	55.9±9.9	
<b>Age Group</b>	<1 Yr	19.8±4.4	<0.0001
	1-9 Yrs	45.0±2.1	
	10+ Yrs	18.2±2.8	
<b>Trial Era</b>	Early	36.2±1.9	0.66
	Late	36.6±3.1	
<b>Sex</b>	M	35.4±2.2	0.51
	F	38.0±2.5	
<b>Lineage</b>	B	37.2±2.1	<0.0001
	T	23.0±4.0	
<b>CNS Status at Diagnosis</b>	CNS-3	14.5±4.5	<0.0001
	CNS-2 & CNS-1	37.7±1.7	
<b>WBC</b>	<50K	41.6±2.0	<0.0001
	>=50K	24.3±2.6	
<b>Race</b>	White	38.5±2.0	0.02
	Hispanic	30.5±3.8	
	Black	30.1±5.9	
	Other	38.1±6.9	
<b>NCI Risk</b>	Standard	50.4±2.4	<0.0001
	High	22.6±2.1	

**Table 5**  
**Multivariate analyses of risk factors associated with survival after relapse: Stratified by Time to and Site of relapse**

Multivariate Analysis of Survival Post Relapse Risk Factors (Stratified by Time to Relapse and Site) (N=1391)		RHR	95% CI
Age Group	1-9 Yrs	---	---
	10+ Yrs	1.373	(1.065, 1.771)
Trial Era	Early	1.056	(0.909, 1.226)
	Late	---	---
Sex	M	1.280	(1.095, 1.497)
	F	---	---
Lineage	B	---	---
	T	1.355	(1.101, 1.664)
CNS Status at Diagnosis	CNS-3	1.501	(1.083, 2.083)
	CNS-2 & CNS-1	---	---
WBC	<50K	---	---
	>=50K	1.151	(0.889, 1.488)
Race	White	0.853	(0.707, 1.030)
	Hispanic	---	---
	Black	0.870	(0.640, 1.182)
	Other	0.774	(0.564, 1.062)
NCI Risk	Standard	---	---
	High	1.593	(1.163, 2.184)