CRANIAL IRRADIATION THERAPY FOR PEDIATRIC T-LINEAGE ACUTE LYMPHOBLASTIC LEUKEMIA: A SYSTEMATIC REVIEW

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Abstract

Pediatric cooperative groups have heterogeneous approaches to cranial irradiation therapy (CRT) for T-lineage acute lymphoblastic leukemia (T-ALL). We performed a systematic review of studies that specified a radiation strategy and reported survival for pediatric T-ALL. Our analysis included 59 publications reporting 75 treatment groups (patient n=5731). Over time, average event-free survival (EFS) was higher by 6% per 5 years ($p<0.001$). Adjusting for year, EFS differed among studies that used different radiation strategies: (a) CRT for all patients: (65%, 95% confidence interval, CI: 61% to 68%); (b) risk-directed CRT (55%, 95% CI: 49% to 62%); (c) CRT for central nervous system (CNS) positive patients only (61%, 95% CI: 50% to 72%); (d) CRT omitted for all (70%, 95% CI: 60% to 80%). Compared to the reference group (CRT for all), studies that administered CRT to CNS positive patients only or omitted CRT completely reported similar EFS in a year-adjusted meta-regression. Intensive asparaginase was associated with higher EFS after adjustment for year ($p=0.003$). CRT may not be necessary with current chemotherapy for T-ALL. However, because these observations are drawn from noncomparative studies, these associations are susceptible to bias and represent a rather weak evidentiary basis for drawing conclusions on the comparative effectiveness of alternative CRT strategies.

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List of Abbreviations

ALL: Acute lymphoblastic leukemia

T-ALL: T-lineage acute lymphoblatic leukemia

CRT: cranial irradiation therapy

CNS: Central nervous system

RCT: randomized controlled trial

IT: intrathecal

TIT: triple intrathecal therapy

IT MTX: intrathecal methotrexate

MIPD: meta-analysis of individualized patient data

EFS: event-free survival

OS: overall survival

Introduction

Cure rates for children with T-lineage acute lymphoblastic leukemia (T-ALL) have improved considerably over the past thirty years with current 5-year event-free survival (EFS) rates that are nearly equivalent to the EFS rates of all but the lowest risk B-lineage ALL patients.[1-4] However, patients with T-ALL have an increased risk of central nervous system (CNS) relapse compared those with B-ALL.[5] CNS prophylaxis is currently delivered with either intrathecal (IT) chemotherapy or IT chemotherapy plus cranial irradiation therapy (CRT).

An individual patient data meta-analysis (MIPD) of randomized controlled trials (RCTs), which began prior to 1994, compared event rates among children with ALL treated with CRT plus IT chemotherapy versus IT chemotherapy alone. Results demonstrated that the addition of CRT to IT chemotherapy resulted in fewer isolated CNS relapses, but did not improve EFS or overall survival (OS).[6] Patients with T-ALL comprised a minority of the patients on each trial and several of the trials did not determine the immunophenotype of the subjects. A recent update of this meta-analysis also concluded that CRT could largely be replaced by intensive systemic and IT chemotherapy. However, the authors acknowledged that the data regarding the optimal CNS prophylaxis were limited for the subset of patients with T-ALL.[7] Nonetheless, on the basis of these results and findings from cohort studies suggesting that the omission of CRT does not adversely impact outcomes, there has been a gradual reduction of the use of CRT for T-ALL patients in an attempt to limit the late effects of radiation therapy, such as secondary malignancies, endocrine abnormalities, and cognitive impairment.[8-10] Currently, approaches to the use of CRT for pediatric T-ALL are variable, with some

cooperative groups administering CRT to all T-cell patients, some omitting CRT in all patients, and some using a risk-stratified approach with a prevailing movement to limit the use of CRT.[3;11-16] However, there is limited comparative evidence on the effectiveness and safety of CRT in pediatric T-ALL in the context of current treatment. We sought to explore the evidentiary basis for the movement to reduce the administration of CRT for pediatric T-ALL by means of a methodologically rigorous synthesis of the totality of the available evidence, based on which we draw principled conclusions.

Here, we report a systematic review and meta-analysis comparing survival data from prospective and retrospective cohort studies in children and adolescents with T-ALL treated with several CRT strategies in order to explore whether CRT improves survival when added to current systemic and IT chemotherapy for T-ALL.

METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting our results.[17] A protocol was developed prior to the conduct of the systematic review and submitted to PROSPERO, an international prospective register of systematic review protocols[18]

Literature search

We searched MEDLINE for studies published from inception to May 30, 2012 that reported randomized and non-randomized trials evaluating CNS directed therapy for T-ALL using free-text and MESH terms (e.g., "acute lymphoblastic leukemia," "drug therapy", "radiotherapy".[18] We consulted a research librarian in specifying the search and crosschecked the search results against lists of studies cited in previously published

narrative reviews on the same topic. We limited results to clinical studies in humans, and used PubMed filters for "child" and "clinical trials". We did not set any language restrictions in searches or during citation screening. Reference lists of relevant studies and review papers were screened to identify additional studies meeting inclusion criteria. The titles and abstracts of studies returned by the search were screened by one investigator (MK). The web-based tool, Abstrackr,[19] (Center for Evidence-based Medicine, Brown University) was used to organize the abstract screen.

Eligibility Criteria and Study Selection

One investigator (MK) reviewed full-text articles to determine if studies met eligibility criteria. Eligible studies included at least 10 participants with T-ALL who were younger than 22 years of age at presentation; we did not use a minimum proportion of T-ALL subjects as a cut-off to determine eligibility. We considered randomized studies that either: (a) compared CNS-directed therapies (such as IT chemotherapy alone vs. IT chemotherapy plus CRT) while treating with an identical systemic chemotherapy "backbone" or (b) compared different systemic chemotherapy strategies while treating with an identical CNS prophylactic strategy. In addition we considered prospective and retrospective cohort studies (comparative or single-group). Studies had to report EFS outcomes at 3 years of follow-up (or longer). We excluded non-English language publications at the full-text screening stage because of resource constraints.

When results for a cohort of subjects were reported in multiple publications the "primary" publication from the study was identified as the first publication reporting EFS for the cohort and was used as the primary source for extraction of data. When details regarding the treatments received or EFS statistics were incomplete in the "primary"

publication, review articles or subsequent follow-up articles were used to obtain the missing data. For 20 cohorts we identified multiple publications reporting results on the same patient population.[4;20-23] In all but two cases the reported data relevant to our analysis were identical. In the two cases, we used data from the primary publication in main analyses, and conducted sensitivity analyses with data from follow-up publications.[20;24;25]

Studies were categorized *a priori* by their CRT strategy as follows: (a) CRT for all patients (studies that administered CRT to $\geq$90% of patients); (b) risk-directed CRT (studies that administered CRT to a subset of patients often stratified by age, white blood cell (WBC) count at diagnosis, and CNS status at diagnosis); (c) CRT for patients with involvement of the CNS with leukemia (CNS positive) at diagnosis only; and (d) CRT omitted for all patients. We generally adopted the outcome definitions applied in each individual study. EFS was most commonly defined as time from the start of treatment to relapse at any site, death during remission, or development of a secondary malignancy. Although the primary outcome was 5-year EFS, we also included a single publication that reported three treatment groups that reported 3-year EFS, given that most relapses for T-ALL patients occur within the first 3 years following the start of treatment.[26] Other outcomes of interest included 5-year OS, CNS relapse rate, bone marrow relapse rate, and combined CNS and bone marrow relapse rate.

Data collection and extraction

We created electronic data extraction forms to capture relevant information. Two investigators (MK and MG) extracted data and each verified the other's extracted

information. Discrepancies were resolved by consensus. We did not contact authors to obtain or confirm information. The following study characteristics and outcomes were extracted from each study: (a) eligibility criteria including age range and diagnosis (T-ALL, T-ALL and T-lineage lymphoblastic lymphoma, or any ALL (T-lineage or B-lineage)); (b) number of patients; (c) CRT strategy; (d) CRT dose; (e) CRT timing (in 3-month intervals); (f) IT chemotherapy administered (methotrexate alone vs. triple IT therapy; the few studies that administered double IT therapy were categorized with triple IT chemotherapy) and number of doses; (g) steroids administered in induction and maintenance; (h) cumulative doses of high-dose methotrexate (defined as any dose $\geq$1 gram/m^2); asparaginase, and anthracyclines (calculated as the sum of daunorubicin and doxorubicin, conversions to daunorubicin or doxorubicin were not performed for the minority of studies that used different anthracyclines); (i) definition of EFS; (j) median follow-up; and (k) outcomes: 5-year EFS, 5-year OS, CNS relapse rate, bone marrow relapse rate and combined (CNS and bone marrow) relapse rate, with their corresponding standard errors.

Assessment of Study Validity / Quality Assessment

In lieu of a scale to assign quality scores to the studies,[27] we assessed the following study-level characteristics, which could help us understand the contribution of CRT to EFS: (a) prospective or retrospective study design; (b) whether the definition of EFS was reported; (c) whether EFS estimates include failures before attainment of remission as outcome events; (d) whether the median follow-up was reported; and (e) whether relapses were categorized by site.

Statistical analysis

We obtained summary 5-year EFS and OS probabilities using an inverse variance random effects model for the corresponding Kaplan-Meier estimates.[28] The asymptotic normality of Kaplan-Meier survival probability estimates is a standard assumption in survival analysis.[29;29] Such estimates and their standard errors were available from the majority of studies reporting information on the outcomes of interest (65 of 75 studies for EFS; all studies for OS). In the small minority of studies that did not report the necessary information, we used a normal approximation for the survival proportion assuming no censoring; the impact of this approximation was investigated in sensitivity analysis (see below).

We assessed between study heterogeneity using Cochran's Q statistic[30] and the I^2 index[31] The Q-statistic was considered statistically significant at $P_Q<0.1$. The I^2 index represents the proportion of between-study heterogeneity that is beyond chance and takes values from 0 to 100%. Higher values indicate greater inconsistency. We conducted subgroup analyses (random effects) and univariate random effects meta-regressions to explore associations between EFS and the following *a priori* selected study-level factors: (a) CRT strategy; (b) IT chemotherapy (methotrexate vs. triple IT chemotherapy); (c) maximum number of IT chemotherapy dose (<10 vs. 10-19 vs. ≥20); (d) high-dose methotrexate (dose ≥ 1 gram/m2) present or absent; (e) intensive asparaginase (≥ 400,000 IU/m^2 or administration of PEG-asparaginase) present or absent; (f) high cumulative dose of anthracyclines (daunorubicin plus doxorubicin total ≥300 mg/m^2) present or absent; (g) induction steroid (prednisone vs. dexamethasone); (h) EFS definition (included

induction failures vs. excluded induction failures vs. definition not reported); (i) the year enrollment started for the study; (j) cumulative dose of asparaginase; (k) cumulative dose of high dose methotrexate; (l) cumulative dose of anthracyclines. When a range of chemotherapy doses was administered for T-ALL patients in a single study we used the maximum dose allowed for our analysis. The meta-regressions generated rate differences in EFS for different levels of categorical variables and for changes in continuous variables. All meta-regression analyses were repeated after adding "year of enrollment start" as a covariate, to account for trends over time.

We performed several sensitivity analyses to assess the robustness of our findings. Specifically, we repeated all analyses: (a) after excluding studies that did not report the standard error of EFS survival probabilities (Appendix 1); (b) after excluding studies that did not report 5-year EFS;[26] (c) after substituting slightly different values for EFS and standard errors from follow-up publications for two publications[20;24;25] in which there were discrepancies between the EFS and standard error from the "primary" publication compared to a follow-up publication; and (d) after excluding the reports from the CCG 1961 trial.[32] This trial administered CRT to CNS positive patients, but reported outcomes only on subjects randomized to receive one of two chemotherapy regimens. Children with CNS disease at diagnosis were excluded from this randomization and not included in the publication. Thus none of the patients in the published report received radiation, however, CNS positive patients at diagnosis were excluded.

All analyses were conducted using Stata version IC/12.1 (Stata Corp., College Station, TX, 2012) and OpenMeta-Analyst,[33] (Center for Evidence-based Medicine,

Brown University). Statistical significance was defined as a two-sided p-value <0.05 for all tests except those for heterogeneity. We did not adjust for multiple comparisons.

Results

Included studies

The search returned 2383 abstracts, 491 of which were considered potentially relevant and were reviewed in full text. Eligible were 59 articles (5731 patients with T-ALL enrolled between 1973 and 2005) describing 75 treatment groups (7 studies reported on more than 1 group; Figure 1, Supplemental Table 1, Supplemental Figure 1, & Supplemental references #1-59).

Event-Free Survival

The overall 5-year EFS rate was 63% (95% CI: 59% to 66%; Figure 2). There was extensive heterogeneity among the treatment studies (I^2=82.4, P_Q<0.001). Slightly more than half of the studies administered CRT to all T-ALL patients (n=42, 56%). A risk-directed approach was applied by 19 (25%), whereas in 7 studies (9 %) CRT was administered to CNS positive patients only. Of note, 7 studies (9%) omitted CRT for all patients. A subgroup meta-analysis and a meta-regression analysis demonstrated that studies in the 4 categories had significantly different mean EFS (omnibus p-value for comparison across all categories= 0.046): CRT for all patients (EFS 63%, 95% CI: 59% to 66%) risk-directed CRT (EFS 58%, 95% CI: 52% to 65%), CRT for CNS positive patients only (EFS 57%, 95% CI: 45% to 0.70%), CRT omitted for all patients (EFS 75%, 95% CI: 67% to 82%), (Figure 2). EFS was higher (absolute rate difference, RD,

12%, 95% CI: 1% to 24%; p=0.03) among studies that omitted CRT for all patients compared to the studies that administered CRT to all patients (the reference group). The change in EFS should not be uncritically attributed to the CRT strategies. Figure 3 shows the CRT strategy by enrollment start year. More current studies are more likely to omit CRT. Recent studies are correlated with higher cumulative doses of asparaginase and high-dose methotrexate and with the administration of a greater number of doses of IT chemotherapy.

EFS was significantly associated with the year study enrollment began ($p<0.001$); in random effects meta-regression average EFS was higher by 6% (95% CI: 4% to 9%) per 5 calendar years (Table 1, Figure 4). The following factors were also associated with higher EFS on univariate analysis: the administration of 10-19 or $\geq$20 doses of IT (RD 14%, 95% CI: 6% to 22% and RD 16%, 95% CI: 6% to 26%, respectively), and intensive asparaginase administration when analyzed as a categorical variable (RD 13%, 95% CI: 4% to 22%) or a continuous variable (RD, per 100,000 IU/m^2, 3% (95% CI: 2% to 5%) (Table 1, Figure 4). There were no significant differences in EFS across the three groups of EFS definitions: EFS definition provided and includes induction failures; EFS definition provided, but does not include induction failures; and EFS definition not reported (omnibus p-value = 0.08).

After adjusting for enrollment year there remained differences in the same direction in EFS by CRT strategy (omnibus p-value= 0.01; Table 1). The adjusted EFS for the reference group, CRT to all patients, was 65% (95% CI: 61% to 68%). Compared to the reference group (CRT for all) the adjusted EFS was significantly worse (55%, 95% CI: 49% to 62%) among studies that used a risk-directed approach to CRT (p=0.002).

The adjusted EFS for the other CRT strategies were similar when compared to the reference group: CRT for CNS positive patients only (EFS 61%, 95% CI: 50% to 72%, p=0.47); CRT omitted for all patients (EFS 70%, 95% CI: 60% to 80%, p=0.29). Compared to the reference group (EFS definition provided and includes induction failures) by year-adjusted meta-regression, treatment groups that did not include induction failures in their EFS definition reported better EFS (RD 12%, 95% CI: 3% to 22%, p=0.01). Intensive asparaginase dosing remained significantly associated with higher EFS compared to non-intensive asparaginase dosing after adjustment for enrollment year (RD 11%, 95% CI: 4% to 19%; p=0.003) (Table 1).

Overall survival

OS data were available for 38 of the 75 treatment groups (51%), which included a total of 3275 T-ALL patients (Supplemental Figure 2). The 5-year summary OS rate was 71% (95% CI: 68% to 75%). OS was similar when stratified by the four CRT strategies: CRT for all (OS 71% 95% CI: 67% to 75%), risk-directed CRT (OS 71%, 95% CI: 62% to 80%), CRT for CNS positive patients only (OS 75%, 95% CI: 69% to 81%), CRT omitted for all patients (OS 80%, 95% CI: 67% to 93%) (Supplemental Figure 3). The number of studies that reported OS data was small in the categories that administered CRT to CNS positive patients only (n=3) and that omitted CRT for all (n=2) (Supplemental Figure 3). In univariate random effects meta-regression OS was higher by 4% (95% CI: 0% to 7%) per every 5 years for more current studies (Supplemental Table 2, Supplemental Fig 4). Higher doses of asparaginase were not associated with OS on univariate or year-adjusted regression analysis (Supplemental Table 2).

Sensitivity analyses

Sensitivity analysis demonstrated that the exclusion of 3 treatment groups reporting 3-year EFS (rather than 5-year EFS) did not influence the results. The results were not affected when re-running the analyses using slightly different EFS estimates and standard errors for the two studies with slightly different reported EFS and standard errors within follow-up publications. Similarly, the exclusion of 10 of 75 treatment groups for which the EFS standard errors were not reported (and had to be calculated with the assumption of complete follow up) did not affect the association of CRT strategy with EFS (year-adjusted meta-regression omnibus p-value=0.02 after excluding these studies).[14;34-41] Finally, analysis after excluding the results from the CCG 1961 trial (n=2 treatment groups) did not qualitatively affect the results of our analyses: CRT for all (EFS 64%, 95% CI: 61% to 68%), risk-directed CRT (EFS 54%, 95% CI: 47% to 61%), CRT for CNS positive patients only (EFS 60%, 95% CI: 49% to 71%), CRT omitted for all patients (EFS 69%, 95% CI: 57% to 81%); year- adjusted meta-regression omnibus p-value=0.02.

Assessment of quality and reporting

A definition of EFS was provided for most treatment groups (n=62, 83%) (Supplemental Table 3). Among treatment groups that defined EFS, 11% (n=7) did not include induction failures as "events." Median follow-up time was provided for two-thirds of the treatment groups (n=50). The sites of relapse (specifically among children treated for T-ALL) were reported only in a minority of treatment groups (n=19, 25%).

Among the studies providing this information, there was variability in the proportion of relapses at different sites by treatment studies (Supplemental Figure 5). Most studies did not explicitly provide the criteria for defining relapse at different sites.

Discussion

This systematic review of cohort studies spanning almost 30 years of clinical research found on average, that the EFS (and OS) for T-ALL improved over time. Yet, over these 30 years, treatment strategies have also changed; CRT has been used universally, selectively, or not at all, and chemotherapies have been used in different composition and intensity. In the absence of comparative trials evaluating CRT in pediatric T-ALL we explored with meta-regression the association between EFS (and OS) and characteristics of CRT or other treatments across the years. We found associations between higher EFS and studies that administered more intensive asparaginase dosing. We also found differences in EFS among studies with different CRT strategies, with mean EFS being generally higher in treatment regimens omitting CRT. These findings persisted even after adjusting for how recently a study was conducted (by means of start of enrollment). While these findings appear consistent with the notion that CRT may not be necessary with current treatments for T-ALL, they are based on meta-epidemiological associations and are therefore susceptible to bias. The evidentiary basis for the current movement to omit CRT in managing T-ALL patients is rather weak, and should be further supported with dedicated syntheses of existing MIPD or with an adequately powered clinical trial.

Prospective cohort studies have demonstrated excellent EFS with varied CRT approaches for T-ALL.[3;11;12;15] This has led to calls to restrict or completely omit CRT for all pediatric ALL patients.[42] We sought to summarize the evidence for this prevailing trend in treatment. In our summary we have no RCTs, not even nonrandomized comparative studies. We have almost 60 manuscripts reporting noncomparative, single arm treatments that have examined various treatment regimens and have been conducted over 30 years. It is well understood that drawing casual inferences form noncomparative studies is precarious, even if there is a "clear signal." We used state-of-the-science methods (random effects meta-regression methods) to understand how clear a signal the single arm trials provide, under the best-case (but implausible) scenario that the comparison is unbiased. We demonstrate that even if one is willing to use this body of evidence for casual evidence, there are no clear signals.

To definitively determine the association of CRT with survival for T-ALL better methodological approaches are needed. An RCT of CRT for T-ALL could determine the treatment effect of CRT when applied to a uniform approach to systemic and IT chemotherapy. However, we are not sure what the optimal comparison groups would be in an RCT. Should CRT for all be compared to omission of CRT for all? Nevertheless data from our analyses may be a good starting point for sample size calculations. For example we found that studies that omitted CRT for all had a mean EFS of 70% whereas those that administered CRT to all had a mean EFS of 65% (both numbers are weighted summaries, adjusted for year). Assuming the above (and for power=85% and two sided alpha=5%) an RCT would need to enroll 2152 patients (1076 per arm) to detect this 6% difference in EFS between the two treatment approaches. It is unlikely that such a trial

will be done because of the large number of patients needed, the time and expense required, and because of preferences for treating with and without CRT among the various international cooperative groups. A more pragmatic approach is to conduct a meta-analysis of individual patient data (MIPD). An MIPD would allow for better estimating if there is a relapse risk reduction with the administration of CRT because patient and treatment level characteristics (such as age, sex, WBC count at diagnosis, cumulative asparaginase, number of intrathecal chemotherapy doses) could be adjusted for in the analysis. An MIPD could be completed more quickly than an RCT and offers an opportunity to align the major stakeholders in ALL therapy to address this important clinical question.

There are several strengths to our systematic review. We performed a comprehensive search that included both prospective and retrospective studies and did not restrict our review to more recent studies or to studies reported by large cooperative groups. Our final dataset included 59 publications of 75 treatment groups and a total of 5731 children with T-ALL. We used consistent selection criteria and explored the association of several *a priori* defined treatment characteristics in addition to CRT strategy with EFS.

Nonetheless, our review is limited in that it is composed primarily of single-arm cohort studies. Importantly, we did not identify any RCTs of alternative CRT strategies that specifically reported outcomes for T-ALL subjects. Our estimates of treatment differences were obtained by indirect comparisons across single group cohorts and are susceptible to confounding by study-level characteristics. As such, our results are primarily hypothesis generating and need to be confirmed in directly comparative studies,

preferably with random assignment of patients to alternative interventions (e.g., different CRT strategies). Because our analysis includes studies performed over four decades and studies conducted in different settings (international cooperative groups as well as single institutions), there is significant heterogeneity in the included populations, treatment protocols, and outcome definitions. We explored this heterogeneity with regression analyses and accounted for unexplained variability through random effects models. Finally, we did not have access to the primary patient data and could only perform regression analyses based on study-level characteristics. An MIPD of T-ALL patients treated on RCTs comparing the addition of CRT to IT and systemic chemotherapy would help evaluate the comparative effectiveness of alternative CRT strategies.

In summary our findings are consistent with similar EFS among studies that administer CRT to all patients, administer CRT to CNS positive patients only or omit CRT for all children with T-ALL. CRT may not necessary for T-ALL patients in the context of modern systemic and IT chemotherapy; however this conclusion cannot be strongly supported on the basis of the available evidence. We encourage investigators to prospectively report the sites of relapse, retrieval rates after relapse by site, secondary malignancy rates, and OS specifically for T-ALL patients on childhood ALL trials so that the contribution of CRT strategy to OS can be better understood. An RCT of CRT for T-ALL or an MIPD would allow for a more conclusive understanding of the effect of CRT strategy on survival for T-ALL.

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Table 1. Unadjusted and adjusted for enrollment year one factor at a time analysis. The association of treatment characteristics with EFS.

Treatment characteristic	Subgroup	N studies	5-yr EFS of reference group (percentage (95% CI)) and absolute rate differences of comparison subgroups (95% CI)	Joint p-value	Adjusted* 5-yr EFS of reference group (percentage (95% CI)) and absolute rate differences of comparison subgroups (95% CI)	Joint p-value
CRT	CRT for all	42	63 (59, 68)	0.046	65 (61,68)	0.01
	Risk-directed CRT	19	- 5 (-12, 3)		-10 (-16, -3)	
	CNS + only	7	-5 (-18, 7)		-4 (-15, 7)	
	No CRT	7	12 (1, 24)		5 (-5, 15)	
IT chemotherapy	MTX	38	63 (58, 68)	0.79	64 (60, 69)	0.12
	TIT	36	-1 (-8, 6)		-5(-11, 1)	
Total doses of IT	0-9	18	52 (45, 59)	0.002	56 (49, 63)	0.17
	10-19	33	14 (6, 22)		8 (-1, 18)	
	>=20	14	16 (6, 26)		9 (-2, 21)	
HD Methotrexate	No HD MTX	24	58 (52,64)	0.07	60 (54, 66)	0.41
	HD MTX	42	7 (-1, 15)		3 (-4, 10)	
Asparaginase	<400,000 IU	50	60 (56, 64)	0.003	59 (56, 63)	0.003
	>=400,000 IU or PEG	14	13 (4, 22)		11 (4, 19)	
Anthracycline	<300 mg/m^2	44	63 (58, 68)	0.88	61 (57, 65)	0.09
	>=300 mg/m^2	19	1 (-8, 9)		6 (-1, 14)	
Induction steroid	prednisone	68	62 (59, 66)	0.50	63 (60, 66)	0.38
	dexamethasone	3	-2 (-20, 17)		-12 (-28, 5)	
	randomized	3	9 (-7, 25)		-2 (-16, 12)	

EFS definition	Includes induction failures	55	61 (57, 64)	0.06	61 (58, 64)	0.08
	Excludes induction failures	7	14 (2, 26)		12 (2,23)	
	Definition not reported	13	4 (-5, 14)		1 (-8, 9)	
Enrollment year	per 5 years		6 (4, 9)	<0.001	N/A	N/A
Asparaginase	per 100,000 IU/m^2		3 (2, 5)	<0.001	3 (1, 5)	0.001
HD Methotrexate	per 5 grams/m^2		1 (-1, 3)	0.27	1 (-1, 2)	0.40
Anthracycline	per 100 mg/m^2		0 (-3, 3)	0.92	2 (-1, 5)	0.22

Legend: *Adjusted for enrollment start year; EFS= event-free survival, CRT=cranial irradiation therapy, IT = intrathecal, HD = high dose, PEG = polyethylene glycosylated (PEG) -asparaginase

Figure 1. Search strategy flowchart.

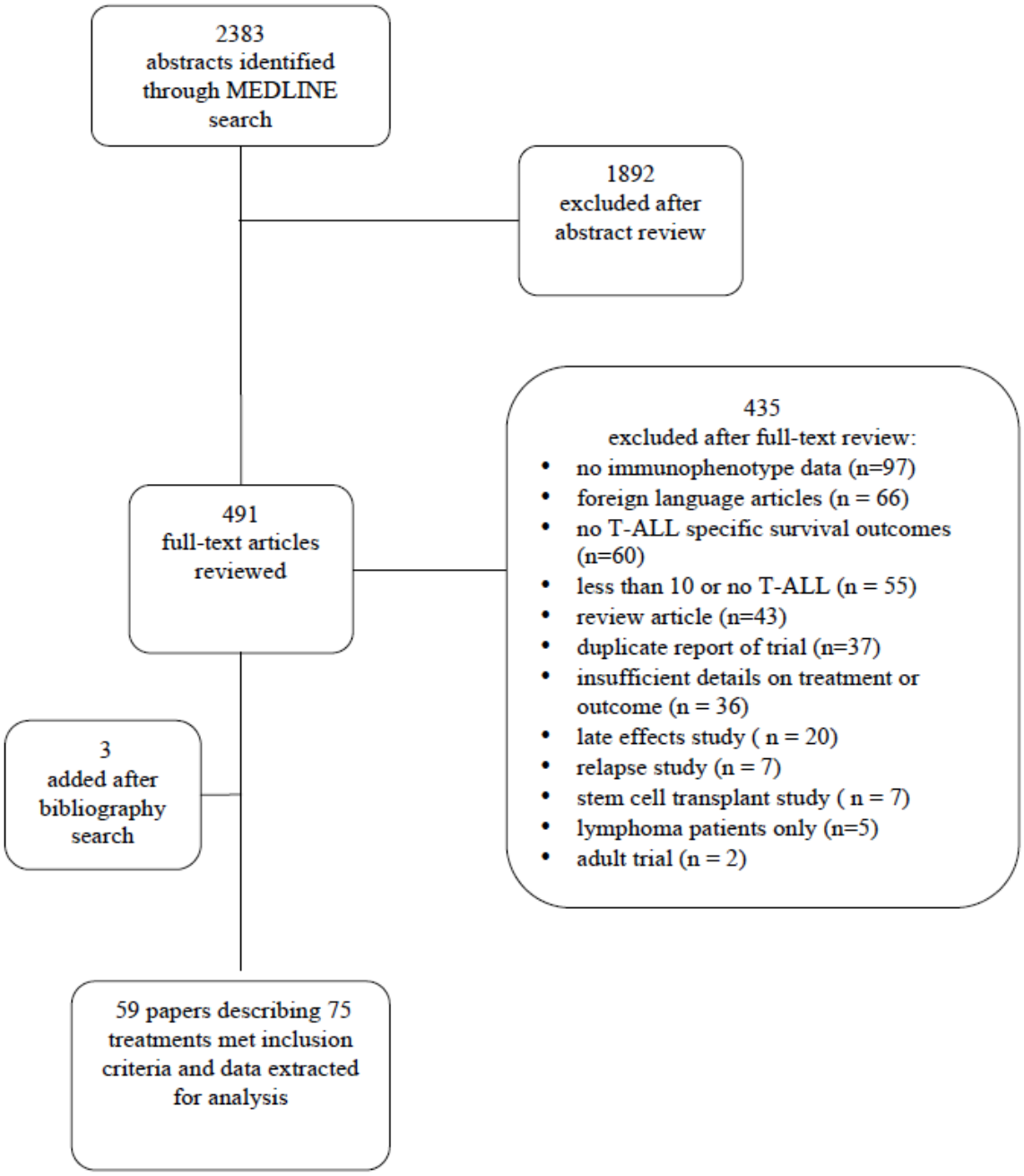


Figure 2. Results of sub-group meta-analyses.

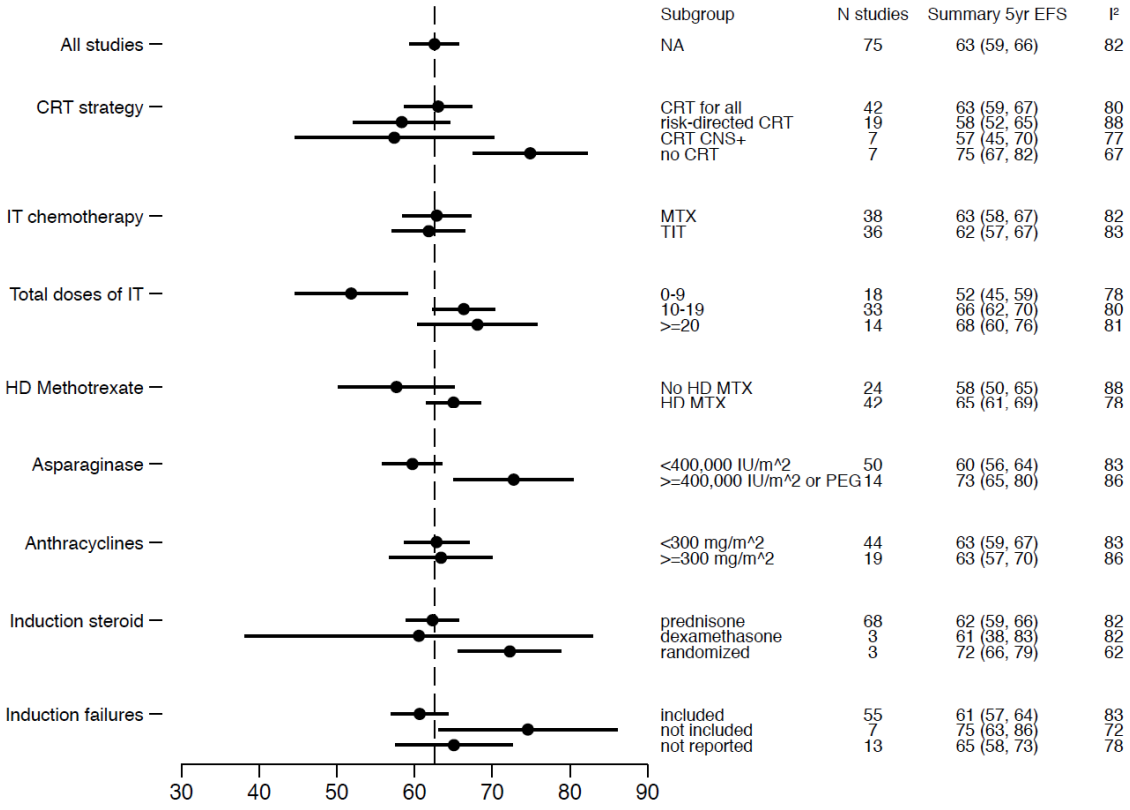
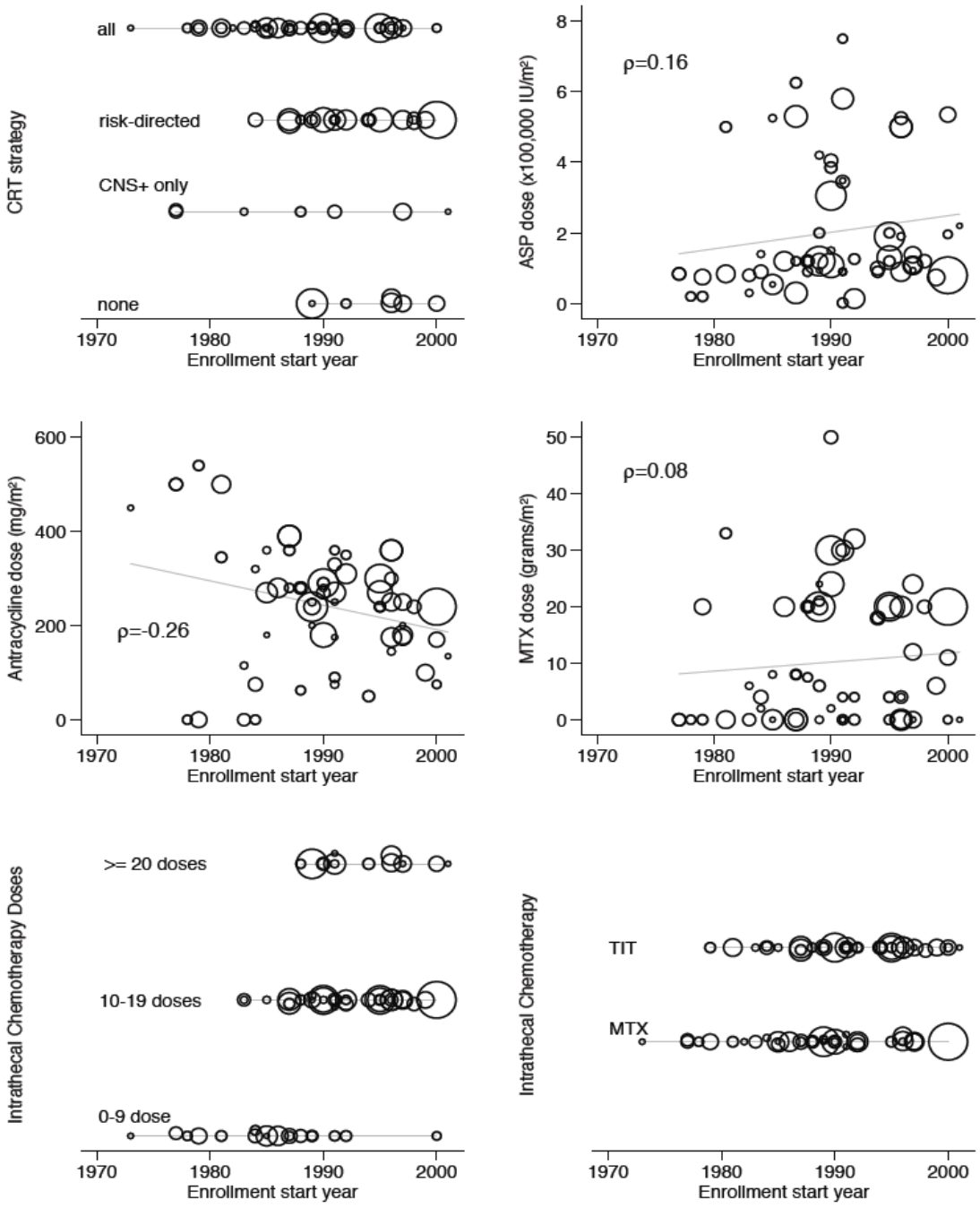
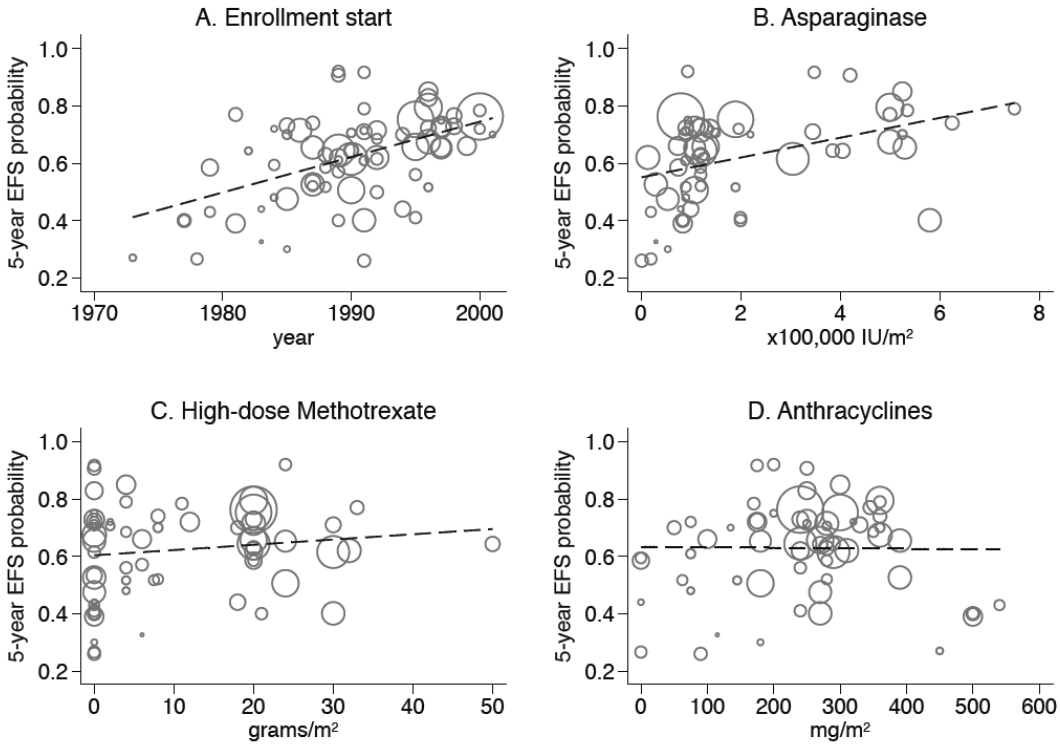


Figure 3. Changes in treatment strategies over time.



Legend: The sizes of the circles are proportional to the sample sizes of the included studies. The p value represents the Pearson correlation coefficient.

Figure 4. Event-free survival meta-regression plots.



Legend. The area of the circles represents the weight of each study in the meta-analysis.

Supplemental Table 1. Characteristics of treatment studies.

Author, Year Study Name	Enrollment Years Design	Eligibility Age Diagnosis	NT-ALL	CRT Dose (Gy) Timing (mo) Strategy (% CRT*)	Median follow-up (yrs)	IT chemo Doses	HDMTX (g/m^2)	Asparaginase (IU/m^2)	Anthracycline** (mg/m^2)	Steroid: Induction/Maintenance
Pullen, 1982[1] SWOG 7615	1977-1979 prospective	0-18 T-ALL	53	NS NS CNS+	3.3	MTX 7+***	0	84,000	350-500	pred/none
Clavell, 1986[2] DFCI 81-01	1981-1985 prospective	0-18 ALL	39	28 Gy 1-2.9 mos All	2.9	MTX 9	4 - 33	500,000+	345	pred/pred
Hitchcock-Bryan, 1986[3] DFCI 73-01	1973-1977 prospective	0-20 ALL	11	24 Gy 1-2.9 mos All	10	MTX 7	NS	NS	450	pred/pred
Lauer, 1987[4]	1978-1981 prospective	NS ALL	30	20-24 Gy 1-2.9 mos All	5.7	MTX 4	0	20,000	0	pred/none
Gruemayer, 1990[5] ALL A 84 protocol	1984-1986 prospective	0-18 ALL	18	12-24 Gy 1-2.9 mos All	3.5	MTX NS	0-2	140,000	320	pred/none
Rivera, 1991[6] Total Therapy XI	1984-1988 prospective	0-18 ALL	62	18-24 Gy 12-15 mos Risk directed NS	3.3	TIT 9	4	60,000 - 90,000	50-75	pred/pred
Falletta, 1992[7] T-cell 2	1977-1986 prospective	0-21 T-ALL	36	15-24 Gy 1-2.9 mos All	NS	TIT NS	0	20,000	540	pred/pred
Falletta, 1992 [7] LSA-L2 plus	1977-1986 prospective	0-21 T-ALL	106	NS NS All	NS	TIT NS	0	84,000	350-500	pred/none
Falletta, 1992[7] LSA2-L2	1977-1986 prospective	0-21 T-ALL	51	NS NS CNS +	NS	MTX NS	0	84,000	350-500	pred/none
Pui, 1992[8] Total Therapy X	1979-1983 prospective	0-19 ALL	51	24 Gy 12-15 mos All	NS	MTX 9	0	80,000	0	pred/none
Lauer, 1993[9]	1983-1988	1-21 HR	19	30 Gy cranial	NS	TIT 18	6	30,000	115	pred/none

POG, 8398	prospect ive	B-ALL & T-ALL		18 Gy spinal 6-8.9 mos CNS +						
Reiter,1994[10] ALL-BFM 86	1986-1990 prospect ive	0-18 ALL	126	12-24 Gy 6-8.9 mos All	5.0	MTX 9	20	120,000	280	pred/none
Schorin, 1994[11] DFCI 85-01	1985-1987 prospect ive	0-18 ALL	20	22-24 Gy 1-2.9 mos All	6.2	DIT 11	0-8	475,000-525,000	360	pred/pred
Chessells, 1995[12] MRC UKALL X	1985-1990 prospect ive	0-14 ALL	138	18-24 Gy 1-2.9 mos All	5.9	MTX 6-8	0	54,000	180-270	pred/pred
Conter, 1995[13] AIEOP ALL 88	1988-1992 prospect ive	0-15 ALL	54	12-18 Gy 3-5.9 mos All	5.7	MTX 9	20	120,000	280	pred/none
Nachman 1997[14] CCG 1882 pilot	1989-1990 prospect ive	1-16+ NCI HR SER	22	18 Gy 1-2.9 mos All	4.4	MTX 13+	0	420,000	250	pred/pred
Conter, 1998[15] AIEOP ALL 91	1991-1995 prospect ive	0-15 ALL	144	12-24 Gy 3-5.9 mos Risk directed 51%	4.4	TIT 12-23	20-30	120,000-580,000	240-270	pred/none
Evans, 1998[16] Total Therapy XII	1988-1991 prospect ive	0-18 ALL	29	18-24 Gy 12-15 mos Risk directed NS	NS	TIT 13-20	7.5	60,000-90,000	50-75	pred/none
Nachman, 1998[17] CCG 1882 augmented arm	1991-1995 prospect ive	1-16+ NCI HR with SER	12	18-24 Gy CSI 1-2.9 mos All	NS	MTX 17-22	0	348,000	175	pred/pred
Nachman 1998[17] CCG 1882 standard arm	1991-1995 prospect ive	1-16+ NCI HR with SER	14	18-24 Gy 1-2.9 mos All	NS	MTX 14-18	0	90,000	250	pred/pred
Pui, 1998[18] Total Therapy XIIIA	1991-1994 prospect ive	0-18 ALL	23	18-24 Gy 12-17.9 mos Risk directe	4.3	TIT 15-26	dose NS	60,000-90,000	75	pred/pred

				d NS						
Amylon, 1999[19] POG 8704 intensive asparaginase	1987-1992 prospective	1-21 T-ALL & LBL	160	24 Gy 3-5.9 mos Risk directed NS	NS	TIT 17	0	530,000	390	pred/pred
Amylon, 1999[19] POG 8704 control	1987-1992 prospective	1-21 T-ALL & LBL	157	24 Gy 3-5.9 mos Risk directed NS	NS	TIT 17	0	30,000	390	pred/pred
Campbell, 1999[20] PINDA 87	1987 1992 prospective	0-15 ALL	29	12-24 Gy 6-8.9 mos All	6.5	MTX 9	4 to 8	80,000 - 120,000	280	pred/none
Kamps, 1999[21] Dutch ALL-7	1988-1991 prospective	0-15 ALL	34	12-18 Gy 6-8.9 mos CNS +	5	MTX 10	20	120,000	280	pred/none
Shing,1999[22]	1985-1992 prospective	0-15 ALL	10	18 Gy 1-2.9 mos All	6.8	MTX 6	0	54,000	180	pred/pred
Conter, 2000[23] AIEOP ALL 87	1987-1991 prospective	1-15 ALL	74	18 Gy 1-2.9 mos All	NS	MTX 9	0	NS	NS	pred/pred
Schrappe, 2000[24] ALL-BFM 90	1990-1995 prospective	0-18 ALL	284	12-24 Gy 3-6 mos All	4.8	TIT 11-14	20 -30	222,000-305,000	240-290	pred/none
Toyoda, 2000[25] L92-13	1992-1995 prospective	1-15 ALL	39	18 Gy 3-6 mos All	4	TIT 8	0	126,000	NS	pred/none
Tsuchida, 2000[26] L84-11	1984-1989 prospective	1-15 ALL	32	24 Gy NS All	NS	TIT 5	dose NS	NS	0	pred/none
Vilmer, 2000[27] EORTC 58881	1989-1998 prospective	0-18 ALL	299	not used	5	MTX 10-20	20	120,000	240	pred/none
Hann, 2001[28] MRC UKALLXI	1990-1997 prospective	1-15 ALL	205	dose NS 1-2.9 mos Risk directed NS	5.8	MTX 13	0-24	54,000 or 108,000 (RCT)	180	pred/pred
Ishii, 2001[29]	1990-1996	0-18 ALL	19	15 Gy 3-6	NS	MTX	2	150,000	280	pred/none

KYCCSG AL90	prospect ive			mos All		14				
Manabe, 2001[30] L89-12	1989-1992 prospect ive	1-15 ALL	43	18 Gy 1-2.9 mos All	7.3	TIT 8-9	6	NS	NS	pred/none
Silverman , 2001[31] DFCI 91-01	1991-1995 prospect ive	0-18 ALL	28	18 Gy 1-2.9 mos All	5	DIT 11	4	750,000	360	pred/dex
Kamps, 2002[32] Dutch ALL-8	1991-1996 prospect ive	0-18 ALL	56	18 Gy 3-5.9 mos CNS +	NS	TIT 9-14	20-30	120,000-345,000	180-330	pred/none
LeClerc 2002[33] DFCI 87-01	1987-1991 prospect ive	0-18 ALL	38	18 Gy 1-2.9 mos All	9.2	DIT 11	0-8	575,000-625,000	360	pred/pred
Yetgin, 2003[34]	1991-1997 prospect ive	0-18 ALL	35	18-24 Gy 1-2.9 mos Risk directe d 74%	6	TIT 3-8	0	1,200-1,800	60-90	pred/pred
Nathan, 2004[35] Toronto sick kids radiation	1983-1999 retrospe ctive	1-4.99 T-ALL	12	18 Gy 1-2.9 mos All	NS	MT X only 15	0	94,000	200	pred/pred
Nathan, 2004[35] Toronto sick kids no radiation	1983-1999 retrospe ctive	1-4.99 T-ALL	12	not used	NS	MT X 18	24	94,000	200	pred/pred
Pui, 2004[36] Total Therapy XIIIB	1994-1998 prospect ive	0-18 ALL	43	18-24 Gy 12-17.9 mos Risk directe d NS	6.6	TIT 18-24	18	60,000-90,000	50	pred/dex
Saarinen-Pihkala, 2004[37] NOPHO HR-ALL	1992-2000 prospect ive	1-15 ALL	133	18 Gy 9-12 mos Risk directe d 58%	NS	MT X 14-17	16-32	14,000	280-310	pred/pred
Winter, 2006[38] POG 9296	1992-1993 prospect ive	1-18 T-ALL & LBL	29	not used	NS	TIT 17	4	25,000 PEG	350	pred/pred
Moghrabi ,2007[39] DFCI 95-	1996-2000 prospect	0-18 ALL	52	18 Gy 1-2.9 mos	5.7	TIT 11	4	525,000	300	pred/pred

01	ive			All						
Arico, 2008[40] AEIOP ALL 95	1995-2000 prospective	0-18 ALL	191	12-18 Gy 3-5.9 mos Risk directed NS	7.3	TIT 7-11	20	80,000-13,000	240-270	pred / randomization of dex for IR in maintenance
Badell, 2008[41] SHOP 94	1994-1998 prospective	1-18 ALL	63	12 Gy 9-12 mos Risk directed NS	7.9	TIT 10	18	100,000	120 + 90 mg/m^2 epirubicine	pred/none
Badell, 2008[41] SHOP 89	1989-1993 prospective	1-18 ALL	35	15-24 Gy 3-5.9 mos Risk directed NS	13	TIT 6-8	21	100,000-200,000	120-180 + 20 mg/^{m2} mitoxantrone	pred/none
Cole, 2008[42]	2001-2005 prospective	2-20 ALL	10	dose NS cranios pinal 12-15 mos CNS +	3.3	TIT 28	0	220,000	135	dex/none
Karachunskiy, 2008[43] Russia ALL-BFM 90m	1995-2002 Prospective	0-18 ALL	39	18-24 Gy 6-9 mos All	7	MTX 13	4	120,000	240	pred/none
Karachunskiy, 2008[43] Russia ALL-MB 91	1995-2002 prospective	0-18 ALL	34	12-18 Gy 6-9 mos All	7	TIT 13	0	200,000	240	dex/dex
Moricke, 2008[44] ALL-BFM 95	1995-2000 prospective	0-18 ALL	277	12-18 Gy 1-2.9 mos All	7.2	TIT 8-11	20	40,000-190,000	240-300	pred/none
Seibel, 2008[45] CCG 1961 standard post induction intensification	1996-2002 prospective	1-21 NCI HR ALL with RER	125	not used	NS	MTX 21-25	0	90,000	175	pred/pred
Seibel, 2008 [45] CCG 1961 intensive postinduction	1996-2002 prospective	1-21 NCI HR ALL with RER	110	not used	NS	MTX 22-27	0	54,000 + 25,000 PEG	250	pred/pred

intensification										
Mitchell, 2009[46] UK ALL 97	1997-2002 prospective	1-18 ALL NS	118	24 Gy 1-2.9 mos Risk directed NS	8	MTX 16	18-24	108,000	180	pred vs. dex RCT/pred vs. dex RCT
Mitchell, 2009[46] UK ALL 97/99	1997-2002 prospective	1-18 ALL	92	24 Gy 1-2.9 mos CNS+	8	MTX SR: 19-23 HR: 22-26	0	108,000	150-250	pred vs. dex RCT/pred vs. dex RCT
Pui, 2009[47] Total Therapy XV	2000-2007 prospective	1-18 ALL	76	not used	4	TIT 16-25	11	535,000	170	pred/dex
Stark, 2009[48] INS 89	1989-1998 prospective	1-18 ALL	84	12-24 Gy 6-8.9 mos Risk directed 21%	15.2	TIT 12-18	20	120,000	240	pred/none
Stark, 2009[48] INS 98	1998-2003 prospective	1-18 ALL	59	12-24 Gy 6-8.9 mos Risk directed 27%	8.1	TIT 12-18	20	120,000	240	pred/dex
Sutton, 2009[49] ANZCCSG VII	1998-2002 prospective	NS ALL	47	18 Gy NS Risk directed NS	NS	NS NS	NS	NS	NS	pred/dex
Veerman, 2009[50] Dutch ALL-9	1997-2004 prospective	0-18 ALL	90	not used	6	TIT 15	12	138,000	175	dex/dex
Escherich, 2010[51] COALL 82	1982 prospective	0-18 ALL	14	16-24 Gy NS All	16.8	MTX NS	NS	NS	NS	pred/none
Escherich, 2010[51] COALL 97	1997 prospective	0-18 ALL	94	12 Gy NS All	6.6	MTX NS	NS	NS	NS	pred/none
Escherich, 2010[51] COALL 92	1992 prospective	0-18 ALL	78	12 Gy NS All	10	MTX NS	NS	NS	NS	pred/none
Escherich,	1985-	0-18	52	16-24	13.7	MT	NS	NS	NS	pred/none

2010[51] COALL 85	1990 prospect ive	ALL		Gy NS All		X NS				
Escherich, 2010[51] COALL 89	1989-1992 prospect ive	0-18 ALL	18	12-18 Gy NS All	11.7	MT X NS	NS	NS	NS	pred/none
Liang, 2010[52] TPOG-ALL-97	1997-2001 prospect ive	0-18 ALL	83	18 Gy NS All	NS	TIT 14-30	20	75,000	0	pred/dex
Nagatoshi, 2010[53] KYCCSG ALL-96	1996-2002 prospect ive	1-15 ALL	21	18 Gy 3-6 mos All	NS	MT X 11-15	4	140,000-190,000	145	pred/dex or pred
Stary, 2010[54] Czech per ALL-BFM 95	1990-1996 prospect ive	1-18	56	12 Gy 3-5.9 mos All	NS	MT X 11-20	20-50	80,000-405,000	240-270	pred/none
Stary, 2010[54] Czech per ALL-BFM 90	1990-1996 prospect ive	1-18 ALL	45	12 Gy 3-5.9 mos All	NS	MT X 11-20	NS	120,000-385,000	240-290	pred/none
Yamaji, 2010[55] JCCLSG ALL2000	2000-2004 prospect ive	1-15 ALL	25	18 Gy 3-6 mos All	5.6	TIT 6	0	196,000	75+	pred/pred
Arya 2011[56]	1992-2002 retrospe ctive	0-15 ALL	60	18 NS All	NS	MT X	NS	NS	NS	NS/NS
Asselin, 2011[57] POG 9404 ALL HDMTX	1996-2001 prospect ive	1-21 T-ALL & LBL	148	18 Gy 3-5.9 mos All	8.7	TIT 11	20	500,000	360	pred/pred
Asselin, 2011[57] POG 9404 ALL control	1996-2001 Prospect ive	1-21 T-ALL & LBL	151	18 Gy 3-5.9 mos All	8.7	TIT 11	0	500,000	360	pred/pred
Schrappe, 2011 AIEOP-BFM [58]2000****	2000-2006 prospect ive	1-18 T-ALL	464	12-18 Gy 3-5.9 mos Risk directe d NS	5.6	MT X 12-18	20	80,000	240	Randomization of pred vs. dex in induction / none
Inukai 2012[59] L99-15	1999-2003 prospect ive	1-18 ALL	91	12-18 Gy NS Risk directe d 49%	3.8	TIT 9-17	6	74,000	100	pred/none

Supplemental Table 1 Abbreviations / Legend: % CRT: the percentage of subjects treated with cranial irradiation; CRT strategy: (i) All: CRT for all patients, (ii)CNS+: CRT for those patients CNS + at diagnosis only, (iii) Risk-directed: CRT to a subset of patients based on clinical features, (iv) None: no patients received CRT; IT chemo: intrathecal chemotherapy; HD MTX: high-dose methotrexate; NS: not stated; MTX: methotrexate; Pred: prednisone; Dex: dexamethasone; mos: months from the start of treatment; TIT: triple intrathecal therapy; DIT: double intrathecal chemotherapy; NCI: National Cancer Institute; HR: high risk; SR: standard risk; RCT: randomized controlled trial; SER: slow early response; CSI: cranial-spinal irradiation; LBL: lymphoblastic lymphoma; PEG: PEG-asparaginase

* The percentage of subjects who received CRT for studies that used a risk-directed approach was calculated when the information was provided.

** Anthracycline: sum of total daunorubicin and doxorubicin administered

*** A "+" indicates that additional doses of chemotherapy were given but not explicitly quantified.

****AIEP-BFM 2000: AIEOP institutions used a risk-stratified approach; BFM centers administered CRT to all T-ALL patients.

Supplemental Table 2. Unadjusted and adjusted for enrollment year one factor at a time analysis. The association of treatment characteristics with OS.

Treatment characteristic	Subgroup	N studies	5-yr OS of reference group (percentage (95% CI)) and absolute rate differences of comparison subgroups (95% CI)	Joint p-value	Adjusted* 5-yr OS of reference group (percentage (95% CI)) and absolute rate differences of comparison subgroups (95% CI)	Joint p-value
CRT	CRT for all	25	70 (66, 75)	0.62	70 (66, 74)	0.87
	Risk-directed CRT	8	1 (-8, 9)		-2 (-10, 7)	
	CNS + only	3	3 (-10, 16)		2 (-11, 14)	
	No CRT	2	10 (-6, 26)		4 (-12, 20)	
IT chemotherapy	MTX	17	70 (64, 75)	0.34	69 (64, 74)	0.73
	TIT	21	3 (-4, 10)		1 (-6, 8)	
Total doses of IT	0-9	6	64 (55, 74)	0.29	68 (58, 78)	0.95
	10-19	18	8 (-2, 19)		2 (-11, 15)	
	>=20	9	8 (-5, 20)		2 (-12, 15)	
HD Methotrexate	No HD MTX	6	66 (56, 76)	0.23	66 (57, 75)	0.38
	HD MTX	25	6 (-4, 17)		4 (-6, 15)	
Asparaginase	<400,000 IU	21	71 (66, 76)	0.30	69 (65, 74)	0.36
	>=400,000 IU or PEG	9	4 (-4, 13)		4 (-5, 12)	
Anthracycline	<300 mg/m^2	22	70 (65, 74)	0.02	68 (64, 73)	0.02
	>=300 mg/m^2	8	10 (1, 18)		9 (1, 17)	
Induction steroid	prednisone	33	72 (68, 75)	0.16	71 (67, 74)	0.11

	dexamethasone	2	-11 (-27, 4)		-15 (-30, -1)	
	randomized	2	8 (-5, 21)		1 (-12, 15)	
EFS definition	Includes induction failures	31	71 (67, 75)	0.40	61 (58, 64)	0.08
	Excludes induction failures	1	8 (-18, 35)		12 (2, 23)	
	Definition not reported	6	6 (-4, 16)		1 (-8, 9)	
Enrollment year	per 5 years		4 (1, 7)	0.02	N/A	N/A
Asparaginase	per 100,000 IU/m^2		1 (-1, 3)	0.42	1 (-1, 3)	0.49
HD Methotrexate	per 5 grams/m^2		0 (-2, 2)	0.75	0 (-2, 2)	0.98
Anthracycline	per 100 mg/m^2		1 (-4, 5)	0.72	0 (-4, 4)	0.97

Legend: *Adjusted for enrollment start year; EFS= event-free survival, CRT=cranial irradiation therapy, IT = intrathecal, HD = high dose, PEG = polyethylene glycosylated (PEG) –asparaginase

Supplemental Table 3. Description of quality measures for included studies.

Author, Year	Study name	Design	EFS include early failures	Median f/u (yrs)	relapses categorized by site
Pullen, 1982	SWOG 7615	prospective	1	3.3	yes
Clavell, 1986	DFCI 81-01	prospective	1	2.9	no
Hitchcock-Bryan, 1986	DFCI 73-01	prospective	1	10	no
Lauer, 1987	Lauer 1987	prospective	1	5.7	no
Gruemayer, 1990	ALL A 84 protocol	prospective	1	3.5	no
Rivera, 1991	Total Therapy XI	prospective	0	3.3	yes
Falletta, 1992	Falletta 1992 LSA2-L2	prospective	1	NS	no
Falletta, 1992	Falletta 1992 T-cell 2	prospective	1	NS	no
Falletta, 1992	Falletta 1992 LSA-L2 plus	prospective	1	NS	no
Pui, 1992	Total Therapy X	prospective	2	9	no
Lauer, 1993	POG 8398	prospective	1	NS	yes
Reiter, 1994	ALL-BFM 86	prospective	1	NS	no
Schorin, 1994	DFCI 85-01	prospective	1	6.2	yes
Chessels, 1995	MRC UKALL X	prospective	0	5.9	no
Conter, 1995	AIEOP ALL 88	prospective	1	5.7	no
Nachman, 1997	CCG 1882 pilot	prospective	2	4.4	no
Conter, 1998	AIEOP ALL 91	prospective	1	4.4	no
Evans, 1998	Total Therapy XII	prospective	2	NS	yes
Nachman, 1998	CCG 1882 augmented arm	prospective	2	NS	no
Nachman, 1998	CCG 1882 standard arm	prospective	2	NS	no
Pui, 1998	Total Therapy XIIIA	prospective	0	4.3	no

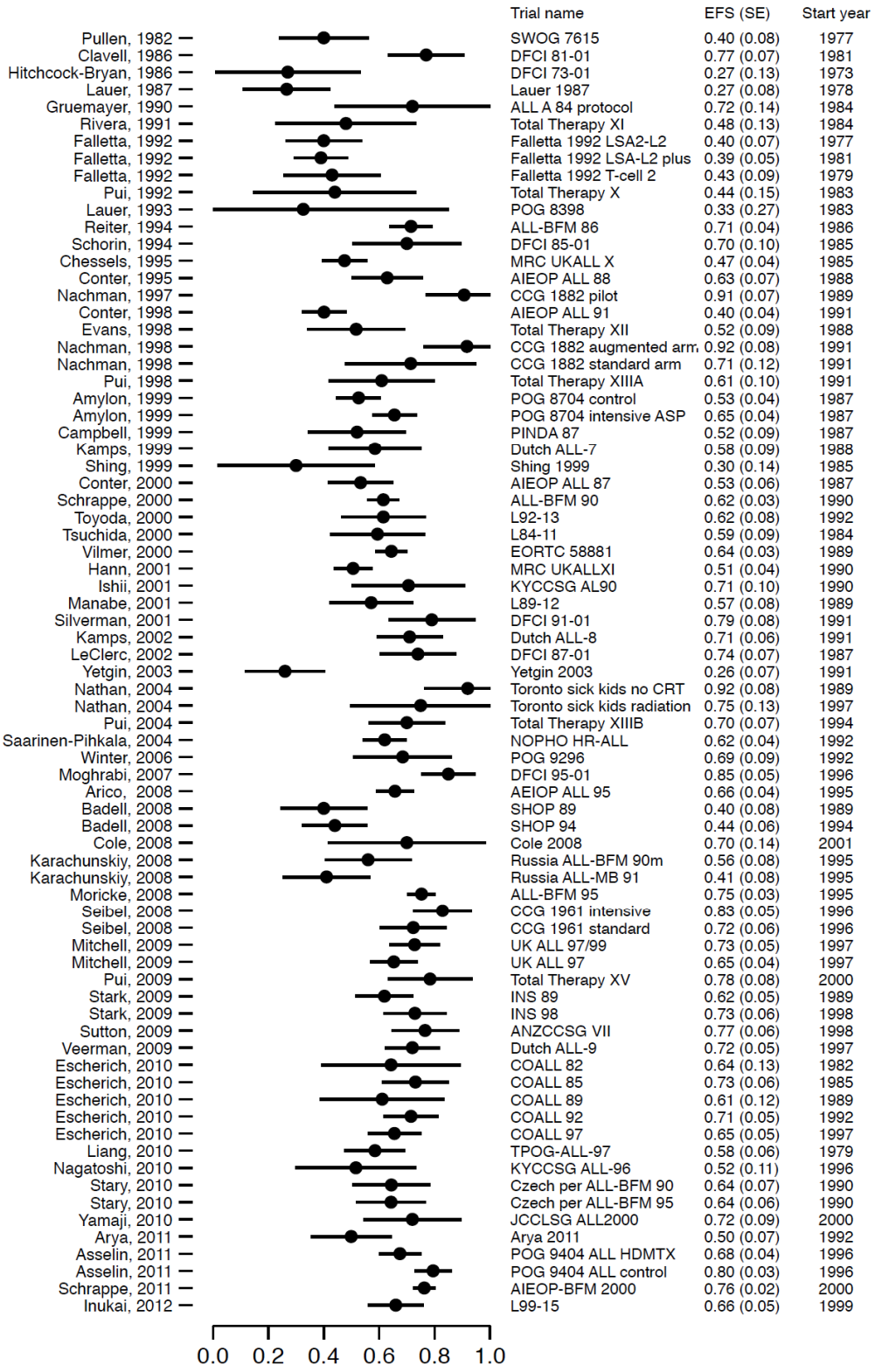
Amylon, 1999	POG 8704 control	prospective	0	NS	yes
Amylon, 1999	POG 8704 intensive ASP	prospective	1	NS	yes
Campbell, 1999	PINDA 87	prospective	1	6.5	no
Kamps, 1999	Dutch ALL-7	prospective	1	5	no
Shing, 1999	Shing 1999	prospective	0	6.8	no
Conter, 2000	AIEOP ALL 87	prospective	1	NS	no
Schrappe, 2000	ALL-BFM 90	prospective	1	4.8	no
Toyoda, 2000	L92-13	prospective	1	4	no
Tsuchida, 2000	L84-11	prospective	1	NS	no
Vilmer, 2000	EORTC 58881	prospective	1	5	no
Hann, 2001	MRC UKALLXI	prospective	1	5.8	no
Ishii, 2001	KYCCSG AL90	prospective	1	NS	no
Manabe, 2001	L89-12	prospective	1	7.3	no
Silverman, 2001	DFCI 91-01	prospective	1	5	no
Kamps, 2002	Dutch ALL-8	prospective	1	NS	no
LeClec, 2002	DFCI 87-01	prospective	1	9.2	no
Yetgin, 2003	Yetgin 2003	prospective	1	6	no
Nathan, 2004	Toronto sick kids no CRT	retrospective	0	NS	yes
Nathan, 2004	Toronto sick kids radiation	retrospective	0	NS	yes
Pui, 2004	Total Therapy XIIIB	prospective	1	6.6	yes
Saarinen-Pihkala, 2004	NOPHO HR-ALL	prospective	1	NS	no
Winter, 2006	POG 9296	prospective	1	NS	yes
Moghrabi, 2007	DFCI 95-01	prospective	1	5.7	no
Arico, 2008	AEIOP ALL 95	prospective	0	7.3	no
Badell, 2008	SHOP 89	prospective	1	13	no

Badell, 2008	SHOP 94	prospective	1	7.9	no
Cole, 2008	Cole 2008	prospective	0	3.3	yes
Karachunskiy, 2008	Russia ALL-BFM 90m	prospective	1	7	no
Karachunskiy, 2008	Russia ALL-MB 91	prospective	1	7	no
Moricke, 2008	ALL-BFM 95	prospective	1	7.2	no
Seibel, 2008	CCG 1961 augmented arm	prospective	2	NS	no
Seibel, 2008	CCG 1961 standard arm	prospective	2	NS	no
Mitchell, 2009	UK ALL 97/99	prospective	0	8	yes
Mitchell, 2009	UK ALL 97	prospective	0	8	no
Pui, 2009	Total Therapy XV	prospective	0	4	no
Stark, 2009	INS 89	prospective	1	15.2	yes
Stark, 2009	INS 98	prospective	1	8.1	yes
Sutton, 2009	ANZCCSG VII	prospective	0	NS	no
Veerman, 2009	Dutch ALL-9	prospective	1	6	no
Escherich, 2010	COALL 82	prospective	1	16.8	no
Escherich, 2010	COALL 85	prospective	1	13.7	no
Escherich, 2010	COALL 89	prospective	1	11.7	no
Escherich, 2010	COALL 92	prospective	1	10	no
Escherich, 2010	COALL 97	prospective	1	6.6	no
Liang, 2010	TPOG-ALL-97	prospective	1	NS	no
Nagatoshi, 2010	KYCCSG ALL-96	prospective	1	NS	no
Stary, 2010	Czech per ALL-BFM 90	prospective	1	NS	no
Stary, 2010	Czech per ALL-BFM 95	prospective	1	NS	no
Yamaji, 2010	JCCLSG ALL2000	prospective	1	5.6	no
Arya, 2011	Arya 2011	retrospective	1	NS	yes

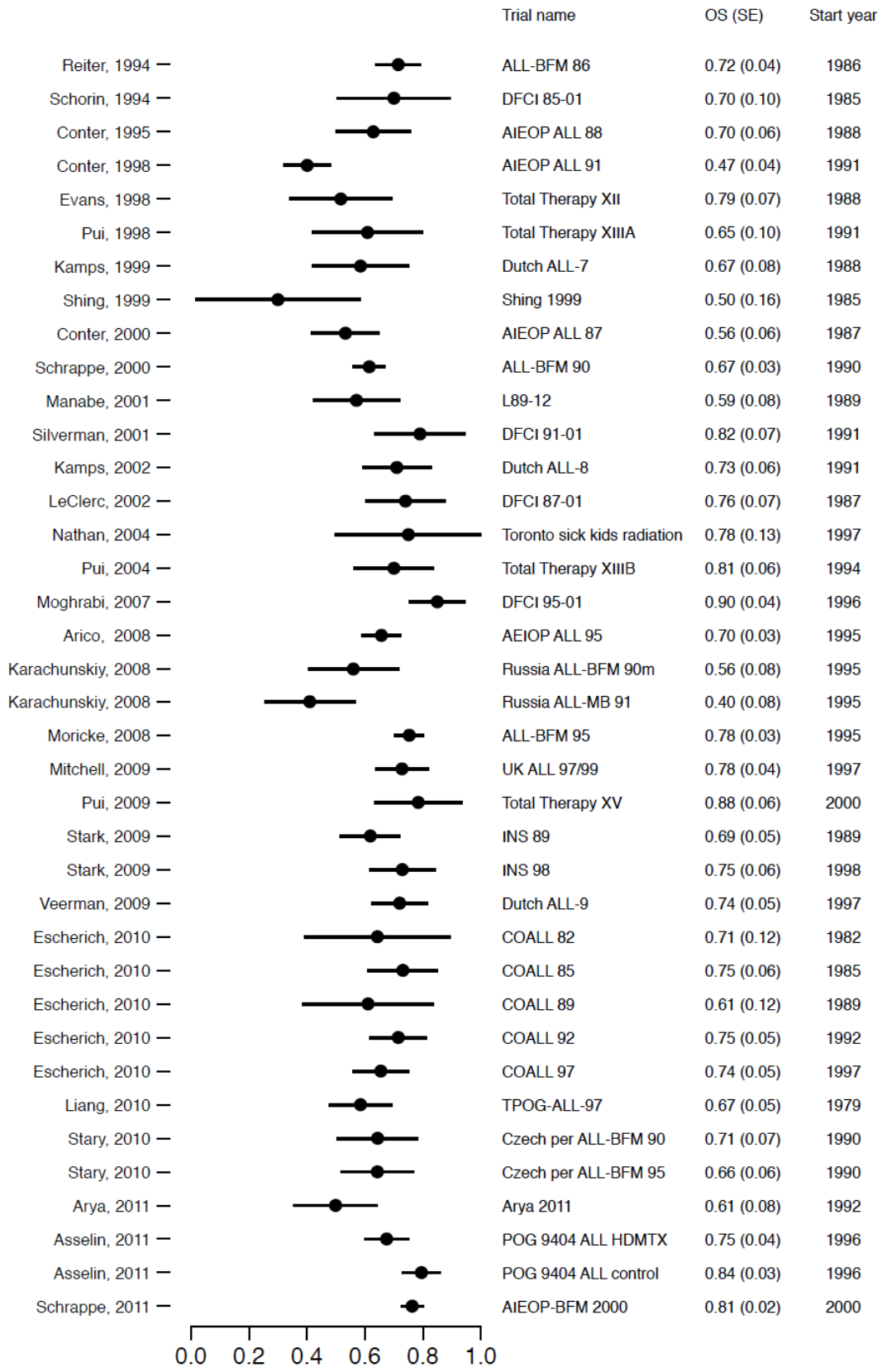
Asselin, 2011	POG 9404 ALL HDMTX	prospective	1	8.7	yes
Asselin, 2011	POG 9404 ALL control	prospective	1	8.7	yes
Schrappe, 2011	AIEOP-BFM 2000	prospective	1	5.6	yes

Legend: 0: EFS definition not reported; 1: EFS definition reported, induction failures included; 2: EFS definition reported, induction failures not included

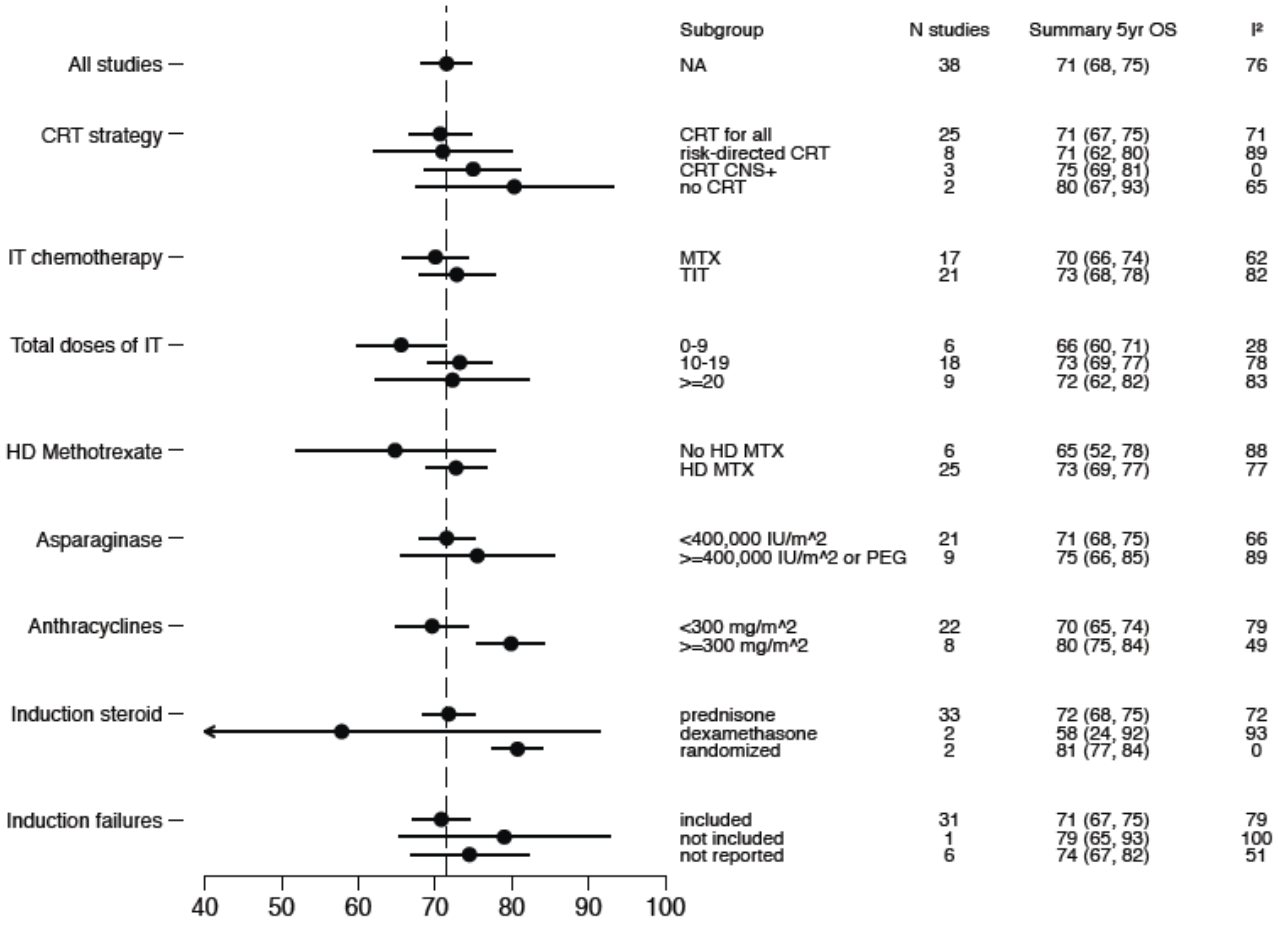
Supplemental Figure 1. Summary 5 year EFS forest plot.



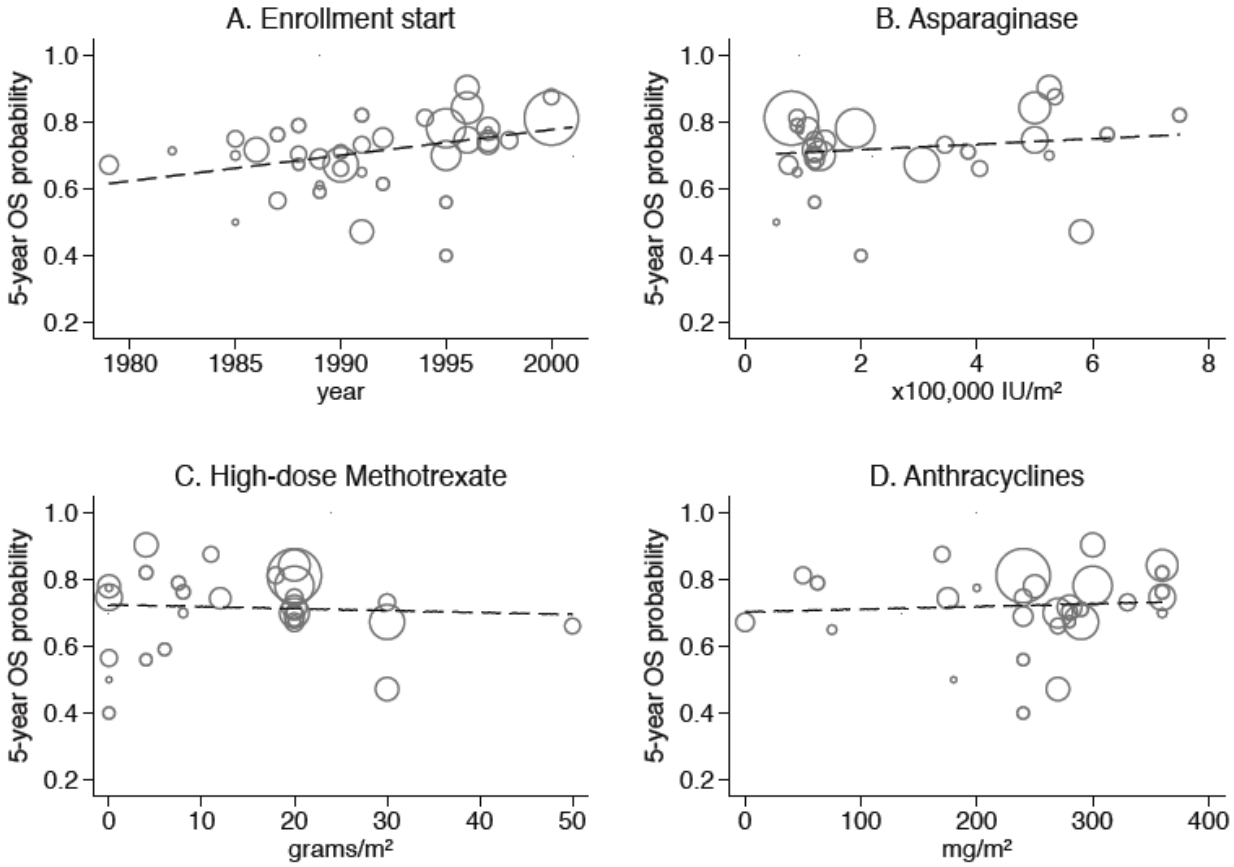
Supplemental Figure 2. Summary 5-year OS forest plot.



Supplemental Figure 3. Overall survival subgroup meta-analyses.

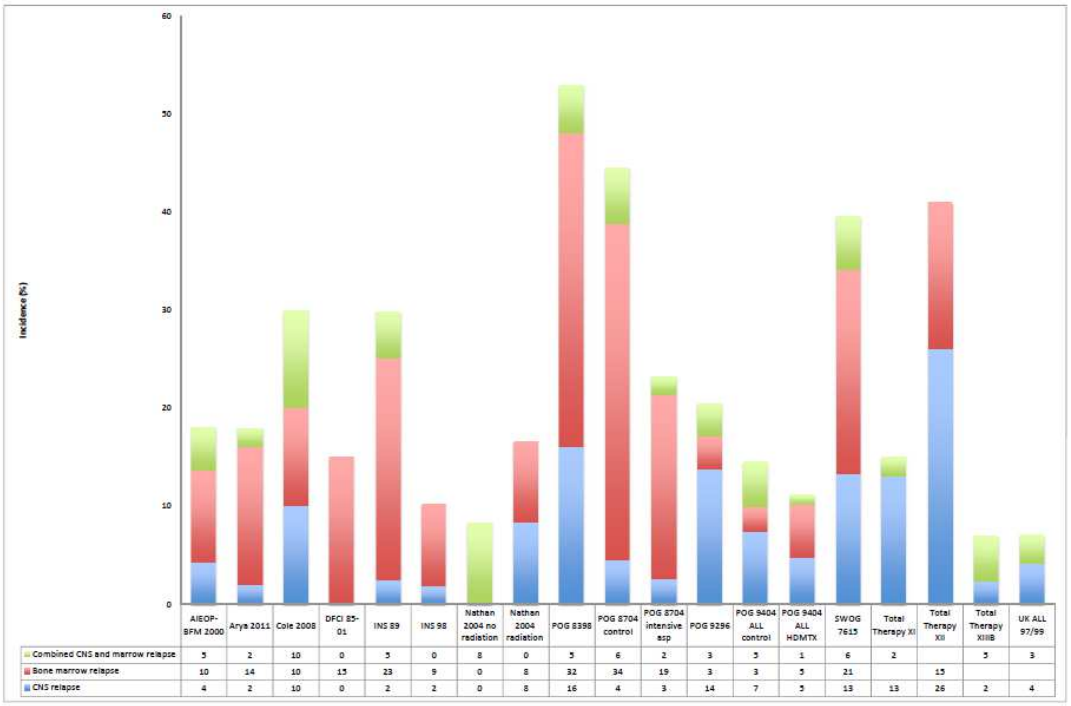


Supplemental Figure 4. Overall survival meta-regression plots.



Legend: The size of the circles is proportional to the sample size of the treatment group.

Supplemental Figure 5. Distribution of sites of relapse for studies that reported relapse by site.



	AIEOP-BFM 2000	Arya 2011	Cole 2008	DFCI 85-01	INS 89	INS 98	Nathan 2004 no radiation	Nathan 2004 radiation	POG 8398	POG 8704 control	POG 8704 intensive esp	POG 9296	POG 9404 ALL control	POG 9404 ALL HDMTX	SWOG 7615	Total Therapy XI	Total Therapy XII	Total Therapy XIIIB	UK ALL 97/99
Combined CNS and marrow relapse	5	2	10	0	5	0	8	0	5	6	2	3	5	1	6	2		5	3
Bone marrow relapse	10	14	10	15	23	9	0	8	32	34	19	3	3	5	21		13		
CNS relapse	4	2	10	0	2	2	0	8	16	4	3	14	7	5	13	13	26	2	4

Legend: Blank boxes indicate that relapse was not reported for that site by the corresponding study.

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