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No clear benefit of preventive cranial radiotherapy in childhood Philadelphia-positive acute lymphoblastic leukemia: a retrospective analysis of the EsPhALL2010 study

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Disclosures

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Contributions

VC, MGV, MS and AB designed the study. AB, VG, MH, VS, MC, C-K L, AA, GE, JS, GC, RP and MS coordinated the clinical study in their own countries or were responsible for data in their group. MGV and PDL performed the statistical analysis. AB, MGV, VC, PDL interpreted the data and wrote the manuscript. All authors read and agreed to the final version of the manuscript.

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Data-sharing statement

Questions regarding data sharing should be addressed to the corresponding author.

In the pre tyrosine kinase inhibitor (TKI) era, i.e. until the early 2000s[1-3] all children and adolescents with Philadelphia positive (Ph+) acute lymphoblastic leukemia (ALL) had indication for cranial radiotherapy (CRT) or hematopoietic cell transplant (HCT) which usually implied total body irradiation in the preparative regimen. The pattern of relapses for patients diagnosed between 1995 and 2005 was well described in a large international study, which showed in 610 patients that 3% had an isolated central nervous system (CNS) relapse, 4% a combined bone marrow (BM) and CNS relapse and 35% an isolated BM relapse.[3]

In the last 2 decades, TKIs have been added on top of chemotherapy with the use of CRT remaining controversial. In the COG AALL0031 study, all 49 patients received CRT and imatinib as TKI. A total of 11 (22%) patients relapsed, 1 in CNS only (2%).[4, 5] In the subsequent COG AALL0622 protocol (opened to recruitment in 2008), dasatinib was given as TKI and CRT was limited to patients with CNS3 disease. Twenty-two (37%) of 60 patients relapsed, 4 (7%) of them with an isolated CNS and 2 (3%) with a combined CNS relapse.[6] Thereafter, in the CA180-372/COG AALL1122 study, dasatinib was given as TKI and HCT indications were further reduced (15% of all patients underwent HCT). CRT was indicated only for patients with CNS3 at diagnosis. Overall, relapses occurred in 38/106 (36%) patients, with isolated CNS relapses in 4 (4%), and combined CNS relapses in 4 (4%).[7]

In the EsPhALL2004, CRT was planned, for all patients not transplanted in first complete remission, at the dose of either 12, 18 or 24 Gys depending on age at the time of CRT and/or CNS involvement at diagnosis. Overall, 160 patients were recruited and 81% of them underwent HCT. Relapses occurred in 50 (31%) patients, with isolated CNS relapses in 5 (3%), and combined CNS relapses in 2 (1%).[8, 9] In the subsequent EsPhALL2010 study (EudraCT 2004-001647-30 and ClinicalTrials.gov, NCT00287105), the fraction of patients who underwent HCT was reduced to 38% (59/155). CRT was prescribed with the same indications of the EsPhALL2004 study. Overall, relapses occurred in 40 (26%) patients, with isolated CNS relapses in 6 (4%), and combined CNS relapses in 11 (7%).[10] Of note, the adherence to CRT prescription in the EsPhALL2010 study was low, particularly in countries where frontline contemporary ALL protocols for Ph negative ALL did no longer use CRT.

In this paper, we report features and outcomes of patients according to whether they received or not the planned CRT in the EsPhALL2010 study, with a causal approach in order to limit the biases caused by the non-randomized comparison. Results support the concept that CRT has no major role in the treatment of Ph+ ALL.

Overall, 155 patients <18 years at diagnosis with Ph+ ALL were enrolled in the EsPhALL2010 study.[10] Patients who underwent HCT (n=59) and those who died or relapsed prior to reaching the CRT phase of the protocol (n=15) were excluded from this study. Thus, 81 patients who survived in complete remission for at least 7 months from diagnosis are described here.

In the EsPhALL2010 study, CRT was planned at the dose of 12 Gy in patients aged 2 years or less and in older patients at 18 or 24 Gy if they did not have or had CNS involvement at diagnosis, respectively. Imatinib was added at the dose of 300 mg/m^2 in all treatment phases. Details of the EsPhALL2010 treatment protocol have already been reported.[10] All patients provided informed consent for participation in the EsPhALL2010 study, which was approved by the ethics committee of each participating institution.

The event-free survival (EFS) was defined as the time from diagnosis to first failure, including resistant disease, relapse, death from any cause, or second malignant neoplasm and overall survival (OS) was calculated as the time from diagnosis to death from any cause. Observation periods were censored at the date of last contact if no event was observed. EFS and OS curves were estimated with the Kaplan-Meier method (with Greenwood standard error) and compared with the log-rank test. The cumulative incidence of relapse (CIR) was estimated accounting for competing risks (all other events) and compared with the Gray test. The Cox regression model and the Wald test were used to evaluate the impact of CRT on EFS

outcome, adjusted by NCI criteria[11]. In order to take into account imbalances in baseline covariates (related either to the choice to administer CRT or to outcome), the primary analysis adopted a causal approach using the inverse probability of treatment weighting (IPTW). A logistic regression model was fitted to estimate the propensity score, i.e. the probability of treatment assignment conditional on observed baseline covariates (i.e. ALL consortia and NCI criteria were regarded as relevant in this setting). Then, the inverse of this probability was used as a weight in an adjusted Kaplan–Meier estimator and log-rank test[12]. Fisher's exact tests (two-sided) were performed to compare patients who did or did not receive CRT, with respect to baseline characteristics. All analyses were performed using SAS version 9.4.

Overall, 81 patients were eligible for CRT. For 15 patients, data on CRT were incomplete and thus 66 were evaluable for outcome by CRT administration (no difference in characteristics and outcome was observed between these 2 groups, data not shown). 28 (42%) did not receive CRT, and 26 of them received additional IT therapy. Presenting features of the two treatment subgroups are described in Table 1. Patients who did not receive CRT (No-CRT group) were more likely to be treated in countries later forming the ALLTogether consortium (p=0.0483) where the use of CRT in frontline ALL protocols for non-Ph+ patients was very limited. No-CRT patients were also likely to be younger (p=0.0002). CNS involvement at diagnosis in the two treatment groups was documented in 3 out of 28 No-CRT patients and in 1 out of 38 CRT patients.

Events are shown in Table 2. Relapses in the No-CRT group occurred in 9 (32%) vs. 15 (39%) patients in the CRT group, including 5 and 4 involving CNS, respectively. There was no advantage in terms of EFS and CIR for patients who received CRT: the 5-year EFS (95% CI) was 64.9% (42.7 – 80.2) vs. 52.3% (33.6 – 67.9, p-value=0.4265) and the 5-year CIR (95% CI) was 35.1% (16.2 – 54.1) vs. 45.1% (27.6 – 62.6, p-value 0.5778) in No-CRT vs. CRT patients, respectively (Figure 1, panels A and C). As shown in Supplementary Figure 1 (panel A), the 5-year OS (95% CI) was 96.2% (75.7 – 99.4) in No-CRT and 71.6% (49.4 – 85.4, p-value=0.0423) in CRT patients. At univariate analysis, type of ALL consortium and age did not significantly affect EFS, while NCI criteria did so, with NCI standard risk patients showing a 5-year EFS of 74.8% (44.9 – 90.0) vs. 50.7% (34.5 – 64.8) in high risk patients (p-value=0.0408, Supplementary Table 1). When analyzed in a multivariable Cox regression model, adjusting by NCI criteria, CRT administration showed no significant impact on outcome: the hazard ratio (HR) of any event for CRT vs. No-CRT was 1.44 (95% CI 0.64 – 3.27, p-value=0.3821), while the HR for NCI high risk vs. standard risk was 2.96 (95% CI 1.01 – 8.64, p-value=0.0477). The description of impact of CRT on EFS, within NCI subgroups, confirms the overall finding of no difference by treatment (Supplementary Figure 2).

The 5-year weighted EFS (95% CI) and CIR (95% CI), based on the IPTW approach, were consistent with unadjusted estimates, being 63.7% (40.1 – 80.1) vs. 51.5% (32.1 – 67.9, p-value 0.4376) and 35.8% (24.9 – 46.8) vs. 44.8% (32.5 – 57.2; p-value=0.5360) in No-CRT vs. CRT patients, respectively (Figure 1, panels B and D). The weighted 5-year OS (95% CI) was 96.9% (73.4 – 99.7) vs. 75.5% (53.0 – 88.3) with a non-significant difference (p-value 0.0854, Supplementary Figure 1, panel B).

Almost half of the patients who had an indication for CRT did not receive it. The outcome of patients who did or did not receive CRT was similar. Isolated CNS relapses occurred only in 2 out of 66 patients, both in the No-CRT group, which however did not contribute to a higher CIR at any sites, including isolated BM relapses. CNS3 disease at diagnosis occurred only in 4 patients and thus no conclusions can be drawn on this issue.

The limitation of this study is in its retrospective and observational nature, as the definition of the two groups of patients receiving or not CRT did not rely on randomization, but on lack of adherence to protocol. This complicated the assessment of treatment effect on outcome, as apparent differences could be due to systematic differences in baseline covariates. The IPTW method was applied to address this issue and led to weighted Kaplan-Meier estimates which confirmed no evidence of benefit of CRT in this context.

In summary, our data support the concept that CRT has no major role in the treatment of Ph+ ALL, which is in keeping with the evidence provided by the Ponte di Legno group on non-Ph+ ALL[13], although it cannot be excluded that there is a potential benefit for patients with CNS disease at diagnosis. The administration of intrathecals and high dose chemotherapy in replacement for CRT allows to spare patients from neuro-cognitive late effects (particularly severe in younger patients) and second malignancies.[14, 15] The omission of CRT may be even more attractive in protocols which adopt dasatinib as TKI and may have additional relevance for patients who need a TBI-conditioning regimen for HCT in second-line treatment.

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Tables

	No CRT		CRT		Overall		
	N	*%*	**N**	*%*	**N**	*%*	**p-value**
Patients analysed	**28**	*100*	**38**	*100*	**66**	*100*	
ALL consortia							*0.0483*
AIEOP/BFM	**9**	*32*	**22**	*58*	**31**	*47*	
ALLTogether	**19**	*68*	**16**	*45*	**35**	*53*	
Gender							*0.4515*
Male	**19**	*68*	**22**	*58*	**41**	*62*	
Female	**9**	*32*	**16**	*42*	**25**	*38*	
Age at diagnosis, years							*0.0002*
< 4	**12**	*43*	**1**	*3*	**13**	*19*	
4 - <10	**9**	*32*	**20**	*52*	**29**	*44*	
≥10	**7**	*25*	**17**	*45*	**24**	*37*	
WBC at diagnosis, $\times 10^9$ cells/L							*0.5411*
< 50	**13**	*46*	**22**	*58*	**35**	*53*	
50 - <100	**7**	*25*	**9**	*24*	**16**	*24*	
≥100	**8**	*29*	**7**	*18*	**15**	*23*	
NCI criteria							
Standard risk	**9**	*32*	**11**	*29*	**20**	*30*	*0.7930*
High risk	**19**	*68*	**27**	*71*	**46**	*70*	
CNS-Involvement							
Yes	**3**	*11*	**1**	*3*	**4**	*6*	*0.3036*
No	**25**	*89*	**37**	*97*	**62**	*94*	

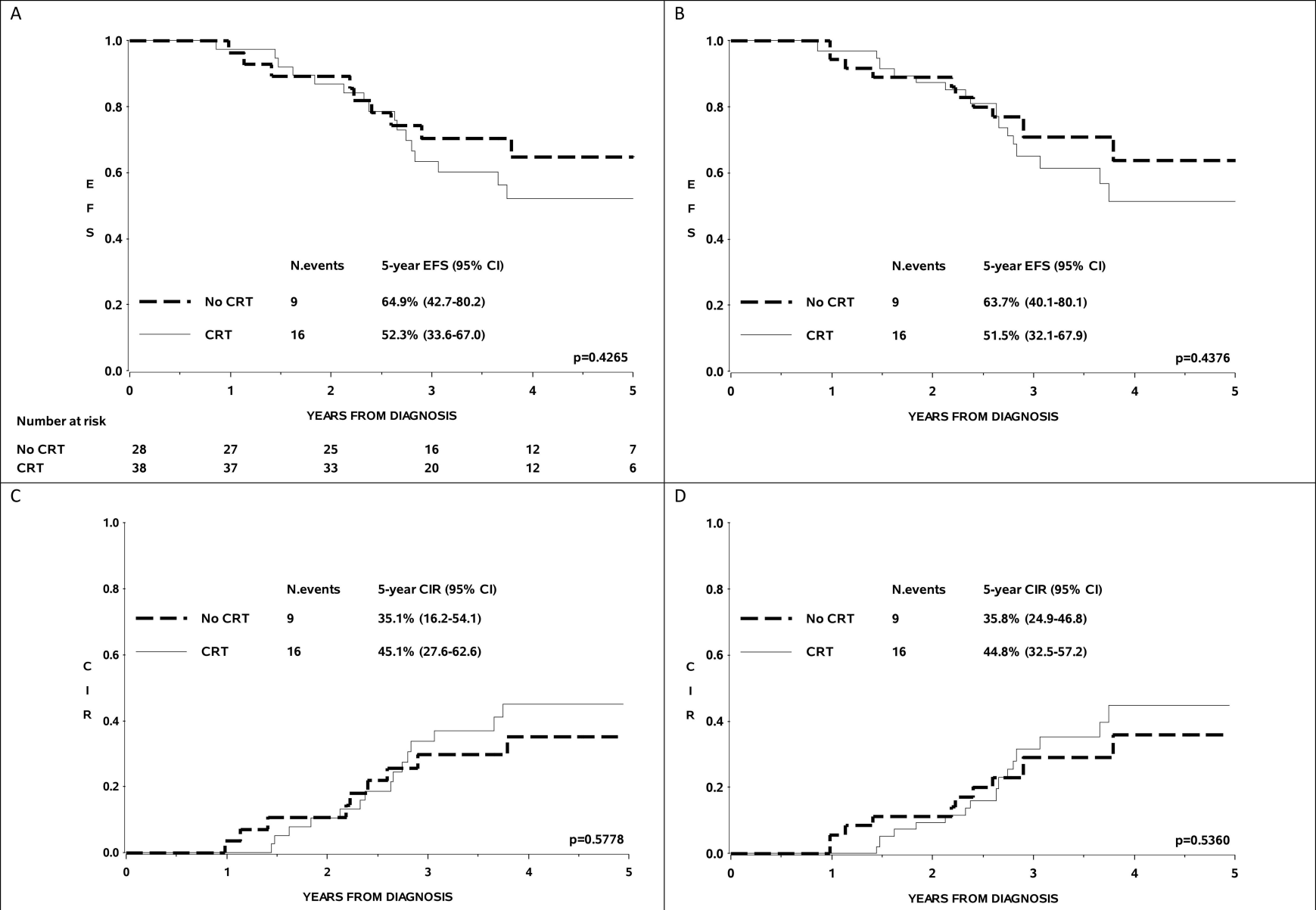
Table 1. Baseline characteristics of 66 patients on chemotherapy at the end of Delayed Intensification I by cranial radiotherapy (CRT) administration. WBC= white blood cell count; NCI criteria: standard risk= patients with WBC<50 x10^9 cells/L and age at diagnosis <10 years; high risk= all other patients; CNS= central nervous system. p-value from Fisher exact test.

	No CRT		CRT		Overall	
	N	*%*	**N**	*%*	**N**	*%*
Patients analysed	28	*100*	38	*100*	66	*100*
Relapses (deaths)	9 (1)	*32 (4)*	15 (7)	*39 (18)*	24 (8)	*36 (12)*
Isolated BM	4		10		14	
BM+CNS	3		4		7	
CNS	2		0		2	
BM+eye	0		1		1	
Deaths in CCR	0	-	1	*3*	1	*2*
Sepsis	0	-	1		1	
CCR	19	*68*	22	*58*	41	*62*

Table 2. Outcome of 66 patients on chemotherapy at the end of Delayed Intensification I, by cranial radiotherapy (CRT) administration. BM= bone marrow, CNS= central nervous system, CCR=continuous complete remission. Four patients had CNS disease at diagnosis: 3 did not receive CRT and 2 relapsed (one in BM and one in BM+CNS), while the remaining patient who received CRT was in CCR at last contact.

Figure legend

Figure 1. Standard Kaplan-Meier estimates of event-free survival (A), weighted Kaplan-Meier estimates of event-free survival (B), cumulative incidence of relapse (C) and weighted cumulative incidence of relapse (D) by cranial radiotherapy (CRT) administration. The initial plateau in the curves reflects the fact that all 66 patients included in the analysis were still in complete remission and on protocol chemotherapy at the planned time of CRT administration (i.e. the end of Delayed Intensification I, about 7 months after diagnosis). The weighted estimates were obtained applying a causal approach based on the inverse probability of treatment weighting.


A
1.0
0.8
0.6
0.4
0.2
0.0
EFS
N.events
5-year EFS (95% CI)
No CRT
9
64.9% (42.7-80.2)
CRT
16
52.3% (33.6-67.0)
p=0.4265
0
1
2
3
4
5
YEARS FROM DIAGNOSIS
Number at risk
No CRT 28 27 25 16 12 7
CRT 38 37 33 20 12 6
B
1.0
0.8
0.6
0.4
0.2
0.0
EFS
N.events
5-year EFS (95% CI)
No CRT
9
63.7% (40.1-80.1)
CRT
16
51.5% (32.1-67.9)
p=0.4376
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YEARS FROM DIAGNOSIS
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1.0
0.8
0.6
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0.2
0.0
CIR
N.events
5-year CIR (95% CI)
No CRT
9
35.1% (16.2-54.1)
CRT
16
45.1% (27.6-62.6)
p=0.5778
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YEARS FROM DIAGNOSIS
D
1.0
0.8
0.6
0.4
0.2
0.0
CIR
N.events
5-year CIR (95% CI)
No CRT
9
35.8% (24.9-46.8)
CRT
16
44.8% (32.5-57.2)
p=0.5360
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YEARS FROM DIAGNOSIS

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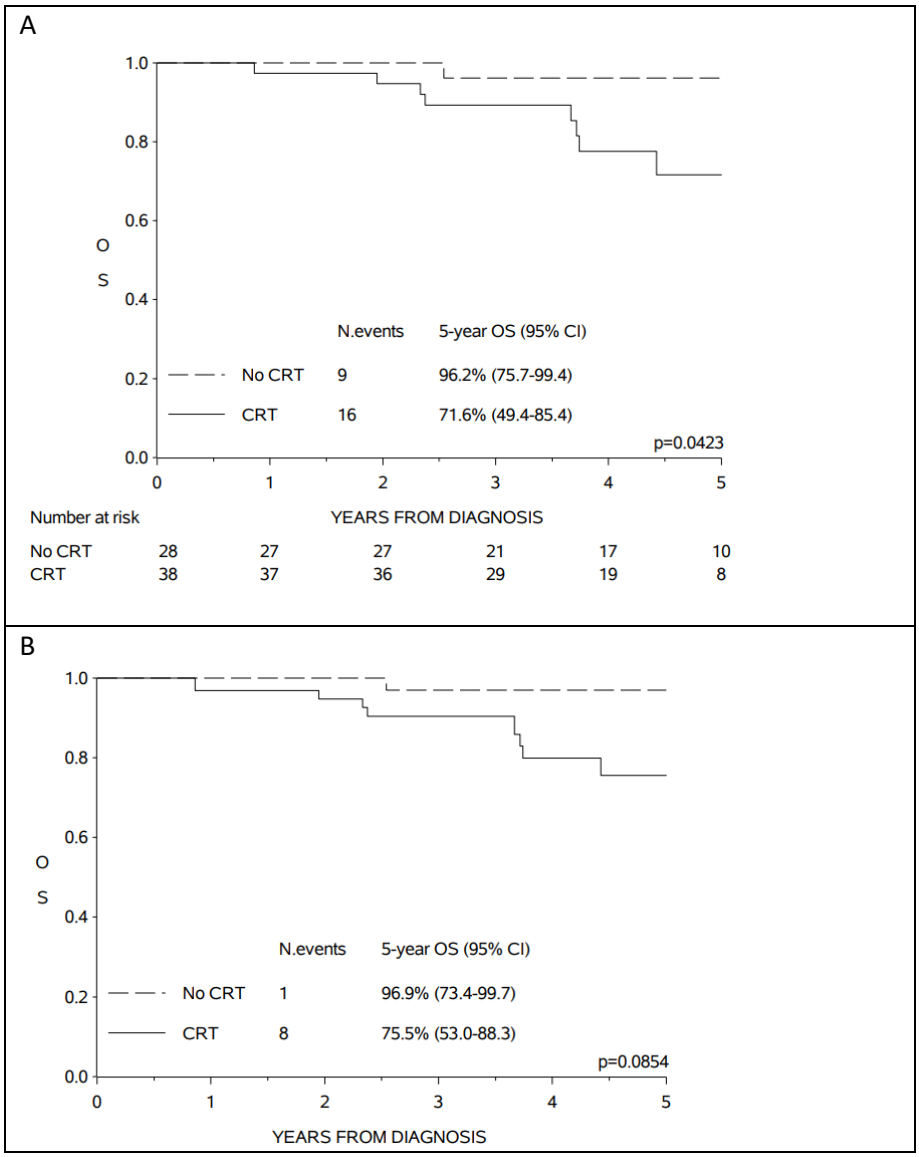
Valentino Conter et al.

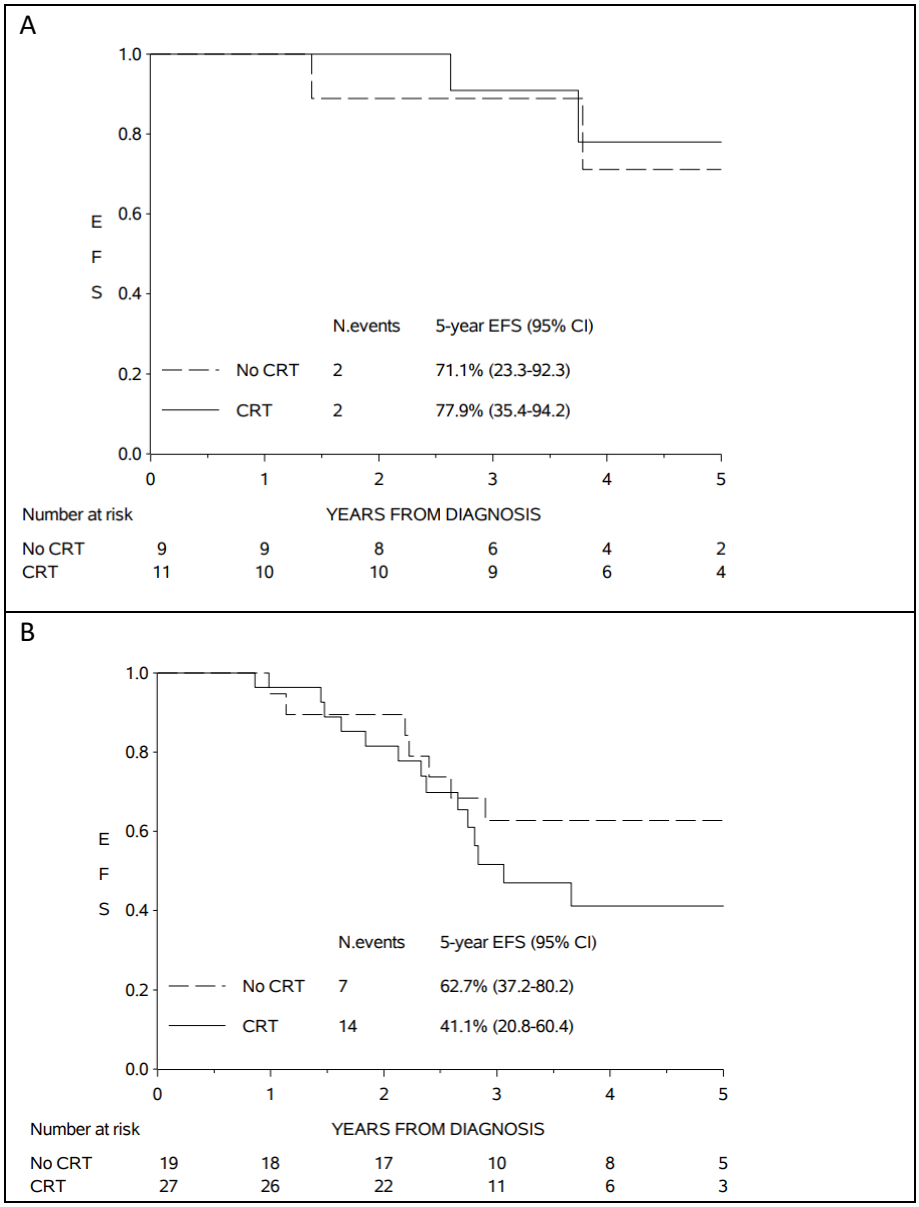
Supplementary material

	N. pts.	N. events	5-year EFS (SE)	95% CI	p-value
Patients analysed	**66**	25			
ALL consortia					*0.8535*
AIEOP/BFM	**31**	11	59.6 (9.8)	38.1 – 75.8	
ALLTogether	**35**	14	56.5 (9.0)	37.3 – 71.8	
Gender					*0.0998*
Male	**41**	13	63.6 (8.4)	44.9 – 77.4	
Female	**25**	12	48.5 (10.5)	27.1 – 66.9	
Age at diagnosis, years					*0.9299*
< 4 years	**13**	6	52.8 (14.1)	23.4 – 75.5	
4 - <10 years	**29**	10	59.6 (10.5)	36.5 – 76.7	
≥10 years	**24**	9	59.4 (10.7)	35.8 – 76.8	
WBC at diagnosis, $\times 10^9$ cells/L					*0.0559*
< 50	**35**	9	68.2 (9.1)	46.9 – 82.4	
50 - <100	**16**	8	48.1 (12.9)	22.4 – 70.0	
≥100	**15**	8	44.0 (13.3)	18.5 – 67.1	
NCI criteria					
Standard risk	**20**	4	74.8 (11.2)	44.9 – 90.0	*0.0408*
High risk	**46**	21	50.7 (7.9)	34.5 – 64.8	
CNS-Involvement					
Yes	**4**	2	-	-	-
No	**62**	23	58.7 (6.8)	44.2 – 70.7	

Supplementary Table 1. 5-year event-free survival (EFS) of 66 patients on chemotherapy at the end of Delayed Intensification I, by baseline covariates. WBC= white blood cell count; NCI criteria: standard risk= patients with WBC<50 x10^9/L and age <10 years; high risk= all other patients; CNS= central nervous system. p-value from log-rank test.



Supplementary Figure 1. Estimate of overall survival (OS) according to the standard Kaplan-Meier approach (A) and to the weighted Kaplan-Meier approach based on the inverse probability of treatment (B), by cranial radiotherapy (CRT) administration. The initial plateau in the curves reflects the fact that all 66 patients included in the analysis were still alive in complete remission and on protocol chemotherapy at the planned time of CRT administration (i.e. the end of Delayed Intensification I, about 7 months after diagnosis).



Supplementary Figure 2. Standard Kaplan-Meier estimates of event-free survival (EFS) in NCI standard risk (A) and high risk (B) patients by cranial radiotherapy (CRT) administration. NCI criteria: standard risk= patients with white blood cell count <50 x10^9/L and age <10 years; high risk= all other patients. The initial plateau in the EFS curve reflects the fact that all 66 patients included in the analysis were still in complete remission and on protocol chemotherapy at the planned time of CRT administration (i.e. the end of Delayed Intensification I, about 7 months after diagnosis).