bjh research paper

Long-term outcome evaluation of medium/high risk acute lymphoblastic leukaemia children treated with or without cranial radiotherapy in the EORTC 58832 randomized study

Caroline Piette,[1] Stefan Suciu,[2] Yves Bertrand,[3] Anne Uyttebroeck,[4] Els Vandecruys,[5] Geneviève Plat,[6] Catherine Paillard,[7] Claire Pluchart,[8] Nicolas Sirvent,[9] Renée Maurus,[10] Maryline Poirée,[11] Pauline Simon,[12] Alina Ferster,[13] Claire Hoyoux,[1] Françoise Mazingue,[14] Robert Paulus,[15] Claire Freycon,[16] Caroline Thomas,[17] Pierre Philippet,[18] Caroline Gilotay,[2] Juttevan der Werff Ten Bosch,[19] Pierre S. Rohrlich[11] and Yves Benoit[5]

[1]Division of Haematology-Oncology, Department of Paediatrics, University Hospital Liège and University of Liège, Liège, [2]EORTC Headquarters, Brussels, Belgium, [3]Department of Paediatric Onco-Haematology, Lyon University Hospital, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France, [4]Department of Paediatric Haematology-Oncology, University Hospitals Leuven, Leuven, [5]Department of Paediatric Haematology-Oncology, Ghent University Hospital, Ghent, Belgium, [6]Department of Paediatric Onco-Haematology, Purpan University Hospital, Toulouse, [7]Department of Haematology, Hautepierre University Hospital, Strasbourg, [8]Department of Paediatric Onco-Haematology, Reims University Hospital, Reims, [9]Department of Paediatric Onco-Haematology, Montpellier University Hospital, Montpellier, France, [10]Department of Paediatric Onco-Haematology, Saint-Pierre Hospital, Brussel, Belgium, [11]Department of Paediatric Onco-Haematology, Nice University Hospital, Nice, [12]Department of Paediatric Onco-Haematology, Besançon University Hospital, Besançon, France, [13]Department of Paediatric Onco-Haematology, Hôpital Universitaire des Enfants Reine Fabiola (ULB), Brussels,

Summary

We investigated the long-term outcome, the incidence of second neoplasms (SN) and the rate of late adverse effects (LAE) in children with central nervous system (CNS) negative medium/high-risk *de novo* acute lymphoblastic leukaemia (ALL), in first complete remission (CR1) at end of late intensification, randomized to receive no cranial radiotherapy (No CRT, $n = 92$) *versus* CRT (standard arm, $n = 84$) in the non-inferiority EORTC 58832 study (1983–1989). Median follow-up was 20 years (range 4–32 years). The 25-year disease-free survival rate ($\pm SE$) was 67·4 ± 4·9% without CRT and 70·2 ± 5·0% with CRT. The 25-year incidence of isolated (6·5 ± 2·6% vs. 4·8 ± 2·3%) and any CNS relapse {8·7 ± 2·9% vs. 11·9 ± 3·5%; hazard ratio (HR) 0·71 [95% confidence interval (CI) 0·28–1·79]; test of non-inferiority: $P = 0·01$} was not increased without CRT. The 25-year SN incidence in CR1 was 7·9 ± 4·6% vs. 11·0 ± 4·2%. The 25-year event-free and overall survival rates were quite similar in both arms [59·5 ± 6·3% vs. 60·5 ± 5·9%, HR 0·94 (95% CI 0·57–1·52), and 78·1 ± 4·3% vs. 78·5 ± 4·5%, HR 1·00 (95% CI 0·53–1·88)]. Omission of CRT was associated with dramatic decrease in CNS and endocrine LAE rates. In conclusion, our data suggest that, with proper systemic and intrathecal CNS prophylaxis, CRT could totally be omitted in CR1 without jeopardizing survival, while decreasing LAE in childhood ALL.

Keywords: childhood ALL, cranial irradiation, survivorship, second neoplasm, late effects.

British Journal of Haematology, 2020, **189,** 351–362

First published online 13 December 2019
doi: 10.1111/bjh.16337

Belgium, [14]*Department of Paediatric Haematology-Oncology, Lille University Hospital, Lille, France,* [15]*CHR Verviers East Belgium, Verviers, Belgium,* [16]*Department of Paediatric Onco-Haematology, Grenoble University Hospital, La Tronche,* [17]*Department of Paediatric Onco-Haematology, Nantes University Hospital, Nantes, France,* [18]*Department of Paediatric Onco-Haematology, CHC, Liège and* [19]*Department of Paediatric Onco-Haematology, Universitair Ziekenhuis Brussel, Brussels, Belgium*

Received 5 July 2019; accepted for publication 23 September 2019
Correspondence: Caroline Piette, Division of Haematology-Oncology, Department of Paediatrics, University Hospital Liège and University of Liège, CHR Citadelle, Boulevard du Douzième de Ligne, 1 – 4000 Liège, Belgium.
E-mail: caroline.piette@chuliege.be

Historically, pre-emptive craniospinal or cranial radiotherapy (CRT) was a standard component of childhood acute lymphoblastic leukaemia (ALL) treatment protocols to prevent central nervous system (CNS) relapses. The emergence of CRT-related neurotoxicity, endocrine sequelae and second neoplasms (SN) prompted several authors to investigate alternative methods of CNS prophylaxis (Green *et al.*, 1980). Systemic and intrathecal chemotherapy could successfully replace CRT in protocols for standard-risk ALL. However, in patients presumed to be at increased risk of CNS relapse, the omission of CRT remained debatable.

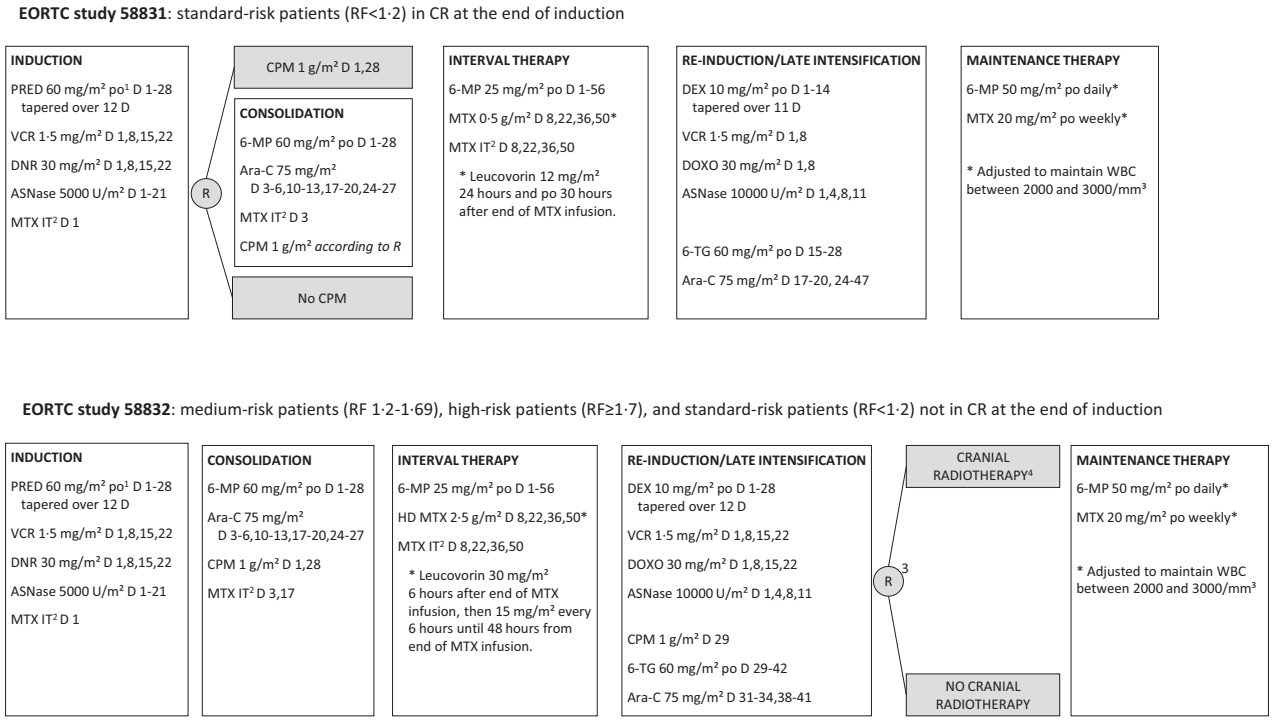
Between 1983 and 1989, we conducted the EORTC studies 58831/2 in order to investigate whether CRT could be omitted in a BFM (Berlin–Frankfurt–Münster)-oriented protocol in which systemic and intrathecal chemotherapy was administered to prevent CNS relapses in patients aged 1–17 years with CNS-negative *de novo* ALL, either standard-risk (study 58831), or medium/high-risk (study 58832) (Fig 1). In 2000, we reported the initial overall results of the efficacy analyses for both studies 58831 and 58832, at a median follow-up of 9·4 years (Vilmer *et al.*, 2000). At 10 years, the disease-free survival (DFS) rate was 67·6% and the incidence of any and isolated CNS relapse was 12% and 7% respectively. In the medium/high-risk group, the patients randomized to receive intermediate-dose methotrexate (MTX) alone (No CRT arm) had similar outcomes to those randomized to receive intermediate-dose MTX followed by CRT.

Here, we provide the long-term outcomes of the randomization comparing No CRT *versus* CRT in medium/high-risk patients included in study 58832, at a median follow-up of 20 years (range 4–32 years). In addition, we evaluated the incidence of SN and the rate of late adverse effects (LAE) by treatment arm. Standard-risk patients included in study 58831 are not part of the present analysis, except for the evaluation of the LAE after different MTX dosages.

Methods

Patient population and treatment protocol

Patients below 18 years with CNS-negative *de novo* ALL were eligible in European Organization for Research and Treatment of Cancer (EORTC) studies 58831/2. Treatment stratification was based on the risk factor (RF) calculation according to Langerman *et al.* (1982). Standard-risk patients (RF < 1·2) received No CRT and were treated with four MTX infusions at 0·5 g/m^2 and six intrathecal MTX injections. Medium- (RF 1·2–<1·7) and high-risk (RF ≥ 1·7) patients in complete remission (CR) at the end of consolidation and still in CR at the end of late intensification were randomized to receive CRT (CRT arm, standard arm) or not (No CRT arm, experimental arm) before the start of maintenance therapy. Dose of CRT was age-dependent: 16 Gy under one year of age, 20 Gy under two years and 24 Gy at



Notes:
[1] Per oral (when not specified, administration is intravenous)
[2] Intrathecal at the dose of 6 mg < 1 year, 8 mg 1-< 2 year, 10 mg 2-<3 year, 12 mg ≥ 3 year
[3] Patients in complete remission at the end of consolidation and still in complete remission after the end of late intensification
[4] Dose according to age : 16 Gy (if age < 1 year), 20 Gy (if age 1-< 2 years) or 24 Gy (if age ≥ 2 years)

Abbreviations: Ara-C: cytarabine, ASNase: asparaginase, CPM: cyclophosphamide, CR: complete remission, D: day, DEX: dexamethasone, DNR: daunorubicin, DOXO: doxorubicin, HD: high-dose, IT: intrathecal, 6-MP: 6-mercaptopurine, MTX: methotrexate, PRED: prednisone, R: randomization, 6-TG: 6-thioguanine, VCR: vincristine, WBC: white blood cells

Fig 1. General scheme of EORTC studies 58831 and 58832.

two years or older. Prophylactic CNS therapy consisted of four intermediate-dose MTX infusions (2·5 g/m^2) during interval therapy and seven intrathecal MTX injections. Details on stratification and treatment protocol are provided in Fig 1.

Data collection

Data were updated by the institutions, based on information reported by the *Belgian Cancer Registry* and the French *Registre National des Hémopathies malignes de l'Enfant* (for vital status and SN) or based on their own medical records (for vital status, disease status, SN and LAE). New medical examination was encouraged but not mandatory.

Definitions

CNS involvement was defined as the presence of at least one blast on cytospin with any white blood cells (WBC) in the cerebrospinal fluid. CNS relapses were categorized as 'isolated' or 'combined' depending on the occurrence of simultaneous relapse at another site. 'Any CNS' relapses included both isolated CNS and combined CNS relapses. 'Bone marrow (BM) combined' relapses were defined as BM relapses occurring simultaneously with another site of relapse, except CNS. SN was defined as any malignancy that occurred after the randomization between CRT and No CRT and distinct from the initial ALL diagnosis, whatever the remission status of the patient. Benign tumours were not considered as SN, except for CNS tumours. Adverse effects were defined with the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. LAEs were defined as adverse effects occurring two months or later after ending first-line therapy or during the first-line therapy (after the end of re-induction/late intensification) and persisting two months or more after ending first-line therapy.

Ethics

At the time of the enrolment in studies 58831 and 58832, informed consent was sought according to local practice of each participating centre and in accordance with the Declaration of Helsinki. The late side effect project (EORTC study 58LAE, ClinicalTrials.gov Identifier NCT01298388) was approved by the Ethical Committee of the University Hospitals and informed consent was obtained from all patients

alive at the time of the latest follow-up, in accordance with the national applicable legislation.

Statistical analysis

Endpoints were disease-free survival [DFS; event: relapse, death in first complete remission (CR1)], incidence of any CNS and of isolated CNS relapses, incidence of SN at any stage and in CR1, event-free survival (EFS; event: relapse without SN, SN in CR1, death in CR1 and without SN), overall survival (OS) from randomization and rate of LAE (defined using the CTCAE 4.0 scale). The expected incidence of any CNS relapse in the CRT arm was 10% at three years. The trial was designed as a non-inferiority trial, for example to test whether in the No CRT arm, compared to the CRT arm, the increase of the three-year incidence of any CNS relapse was ≥10% (null hypothesis) or <10% (alternative hypothesis). In case the latter hypothesis was confirmed, the treatment hazard ratio (HR) would be <2·12.

Distributions of composite time-to-event endpoints were estimated according to the Kaplan–Meier technique and standard errors (*SE*) of the 25-year estimate rates were obtained via the Greenwood formula. The estimated HR and its 95% or 99% confidence interval (CI) were computed using the Cox model. The cumulative incidence of CNS relapse and of isolated CNS relapse, subdistributions of DFS, the cumulative incidence of SN, subdistribution of survival without SN, and the cumulative incidence of SN in CR1 and subdistributions of EFS were computed using competing risk methods (Kalbfleisch & Prentice, 2002). The estimated HR of the subdistributions and its 95% CI were computed using the Fine–Gray model. Only for the CNS incidence a statistical inference was performed; for all others, descriptive statistics were provided. Being a non-inferiority trial (No CRT *versus* CRT), all analyses were based on the per-protocol treatment population: all eligible patients who started the treatment allocated by randomization. SAS 9.4 statistical software (Cary, NC, USA) was used.

Results

A total of 189 patients were randomized in the intent-to-treat (ITT) study 58832. Among them, 183 were eligible (three ineligible patients in each arm) and 176 patients were included in the present per-protocol treatment (PPT) evaluation (one inevaluable patient in the No CRT arm *versus* six in the CRT arm): 92 patients in the No CRT arm and 84 patients in the CRT arm (Fig 2). Clinical characteristics were well balanced in both treatment arms, both in the ITT (data not shown) and PPT populations (Table I). For the entire PPT population, the sex ratio M/F was 1·5, the median age at diagnosis was four years, and the median age at last follow-up was 22 years. Immunophenotyping was not available to distinguish B- and T-ALL.

The 25-year DFS rate (±*SE*) was similar in both arms (67·4 ± 4·9% without CRT vs. 70·2 ± 5·0% with CRT, Fig 3A, Table I). No relapse occurred after seven years. The 25-year incidence (±SE) of isolated CNS relapse was 6·5 ± 2·6% vs. 4·8 ± 2·3% in the No CRT and CRT arms and the 25-year incidence (±*SE*) of any CNS relapse was 8·7 ± 2·9% vs. 11·9 ± 3·5% respectively (Fig 3A, Table I). Comparison of the incidence of any CNS relapse between No CRT and CRT yielded a HR of 0·71 (95% CI 0·28–1·79), which was significantly lower than 2·12 (test for non-inferiority: one-sided $P = 0{\cdot}01$), indicating that the increase of the any CNS relapse incidence without CRT was lower than 10%.

The 25-year SN incidence (±SE) at any time and in CR1 was 7·3 ± 4·3% without CRT vs. 13·0 ± 4·6% with CRT, and 7·9 ± 4·6% without CRT vs. 11·0 ± 4·2% with CRT respectively (Table I). In the No CRT arm, 4 patients out of 92 (4·3%) had SN vs. 9 out of 84 (10·7%) in the CRT arm. Clinical characteristics, SN latency and types, and therapy given as part of ALL or SN therapy are shown in Table II. No children below the age of two at diagnosis developed SN. Patients with SN were mostly females (F/M ratio: 1·6). The latency between randomization and SN diagnosis was shorter for haematological malignancies (median 2·8 years, range 0·5–6·4 years) than for solid tumours (median 21·2 years, range 12·7–28·6). Two patients had acute myeloid leukaemia (AML) at 1·5 and 4·0 years after randomization. In both cases, the fingerprint of a secondary leukaemia (t11q23, monosomia 7, 5q-) was lacking. The difference in SN incidence between both arms was mainly due to a high incidence of meningiomas in the CRT arm (four patients had meningioma as first SN, one of them had a second meningioma and one additional patient had a meningioma after a first AML). Noteworthy, all of them occurred after very long follow-up (range 19·2–28·6 years from randomization). Second or synchronous SN were exclusively observed in patients treated with CRT, in first- or second-line treatment. One patient with malignant histiocytosis died of SN, all others were alive at last follow-up.

The 25-year EFS rate (±*SE*) was similar in both arms: 59·5 ± 6·3% without CRT vs. 60·5 ± 5·9% with CRT (Fig 3B, Table I) as well as the 25-year OS rate (±*SE*): 78·1 ± 4·3% and 78·5 ± 4·5% respectively (Fig 3C, Table I).

Data regarding LAE were available for around 25% of the patients (Table III). Omission of CRT was associated with dramatic decrease in the rate of CNS LAE. Leukoencephalopathy was reported in 8·7% of the patients ($n = 2$) randomized in the No CRT arm but who received second-line treatments comprising CRT or total body irradiation (TBI) vs. 19·2% ($n = 5$) in the CRT arm. Cognitive disturbance was reported in 18·8% of the patients in the No CRT arm ($n = 3$, two in CR1 and one after a BM relapse treated with CRT) vs. 42·1% in the CRT arm ($n = 8$). Seizures occurred in 3·7% of the patients in the No CRT arm ($n = 1$, hereditary epilepsy) vs. 14·3% in the CRT arm ($n = 4$). In

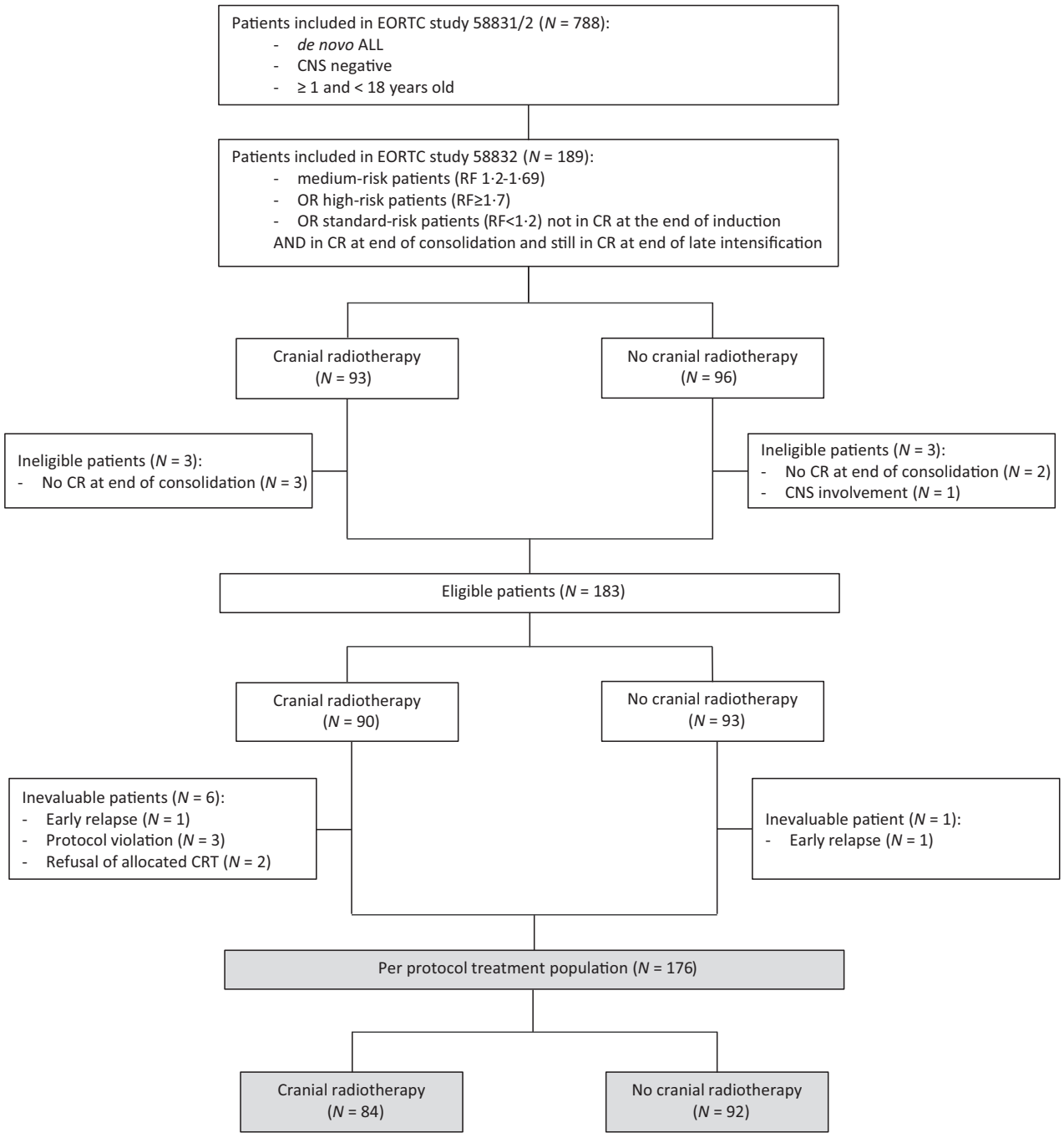


Fig 2. Consort diagram of EORTC study 58832.

the CRT arm, convulsions were secondary to meningiomas (n = 2), to bilateral subdural effusions after CNS relapse (n = 1) or to severe encephalopathy occurring during CRT (n = 1). Finally, strokes were only reported in the CRT arm (7·7% of the patients, n = 2), at 6 and 24 years after end of treatment.

As late neurotoxicity could also be related to intermediate-dose MTX, we compared the rate of LAE in patients randomized for No CRT and treated with intermediate-dose MTX in study 58832, with that of standard-risk patients treated without CRT and with lower dosage of MTX (0·5 g/m^2) in study 58831 (Fig 1). Decrease in MTX dosage was associated with lower rates of leucoencephalopathy (1·6%) and cognitive disturbance (6·3%) (Table III). Seizures were reported in 10·9% of the standard-risk patients (n = 11). In four patients, the convulsions occurred during maintenance therapy, without evident aetiology, except in one patient in whom a hypodense lesion of the left parietal lobe was identified on a computed

Table I. Distribution of the clinical and disease characteristics and of the outcome, according to the treatment arm (No CRT *versus* CRT) in EORTC study 58832.

	No CRT 92 (100%)	CRT 84 (100%)
Sex		
Male, *n* (%)	59 (64·1)	47 (56·0)
Female, *n* (%)	33 (35·9)	37 (44·0)
Age at diagnosis (years)		
<1, *n* (%)	3 (3·3)	4 (4·8)
1–<2, *n* (%)	14 (15·2)	9 (10·7)
2–5, *n* (%)	34 (37·0)	34 (40·5)
6–9, *n* (%)	26 (28·3)	24 (28·6)
≥10, *n* (%)	15 (16·3)	13 (15·5)
Median (range)	4·0 (0–17)	3·5 (0–15)
WBC ($\times 10^9$/l)		
<50, *n* (%)	61 (66·3)	48 (57·1)
50–<100, *n* (%)	13 (14·1)	21 (25·0)
≥100, *n* (%)	18 (19·6)	15 (17·9)
Median (range)	36·3 (1·8–650)	37·5 (3·6–550)
NCI risk group		
Standard risk, *n* (%)	50 (54·3)	41 (48·8)
High risk, *n* (%)	42 (45·7)	43 (51·2)
EORTC risk group		
Standard risk (RF < 1·2), *n* (%)	1 (1·1)	0 (0·0)
Medium risk (RF 1·2–<1·7), *n* (%)	79 (85·9)	74 (88·1)
High risk (RF ≥ 1·7), *n* (%)	12 (13·0)	10 (11·9)
EFS status		
Alive, in CR1, without SN, *n* (%)	59 (64·1)	52 (61·9)
Relapse, *n* (%)	28 (30·4)	24 (28·6)
Any CNS, *n* (%)	8 (8·7)	10 (12·0)
CNS isolated, *n* (%)	6 (6·5)	4 (4·8)
CNS combined, *n* (%)	2 (2·2)	6 (7·2)
BM isolated, *n* (%)	15 (16·3)	10 (11·9)
BM combined (non-CNS), *n* (%)	2 (2·2)	2 (2·4)
Other only, *n* (%)	3 (3·3)	2 (2·4)
SN in CR1, *n* (%)	3 (3·3)	8 (9·5)
SN still alive, *n* (%)	3 (3·3)	7 (8·3)
SN followed by death, *n* (%)	0 (0·0)	1 (1·2)
Death in CR1, without SN, *n* (%)	2 (2·2)	0 (0·0)
DFS		
25-year rate, % (±SE)	67·4 (±4·9)	70·2 (±5·0)
HR (95% CI)	1·08 (0·63–1·83)	
SN in CR1		
25-year incidence, % (±SE)	7·9 (±4·6)	11·0 (±4·2)
HR (95% CI)	0·35 (0·09–1·33)	
EFS		
25-year rate, % (±SE)	59·5 (±6·3)	60·5 (±5·9)
HR (95% CI)	0·94 (0·57–1·52)	
Survival/SN status		
Alive without SN, *n* (%)	68 (73·9)	58 (69·0)
SN, *n* (%)	4 (4·4)	9 (10·7)
Death without SN, *n* (%)	20 (21·7)	17 (20·3)
SN		
25-year incidence, % (±SE)	7·3 (±4·3)	13·0 (±4·6)
HR (95% CI)	0·43 (0·13–1·41)	
Survival status		
Death due to any cause, *n* (%)	20 (21·7)	18 (21·4)
OS		
25-year rate, % (±SE)	78·1 (±4·3)	78·5 (±4·5)
HR (95% CI)	1·00 (0·53–1·88)	

BM, bone marrow; CI, confidence interval; CNS, central nervous system; CR1, first complete remission; CRT, cranial radiotherapy; DFS, disease-free survival (event: relapse, death in CR1); EFS, event-free survival (event: relapse, SN in CR1, death in CR1 and without SN); HR, hazard ratio; OS, overall survival; SN, second neoplasm; WBC, white blood cells.

tomography scan. In four patients, seizures occurred in CR1, 1–6 years after the end of first-line treatment, without clear explanation. Convulsions were reported during the treatment of CNS relapse in three other patients.

Omission of CRT was associated with a decreased rate of endocrine LAE (Table III). The rate of growth hormone (GH) deficiency was 18·5% in the No CRT arm vs. 53·1% in the CRT arm. Hypothyroidism or precocious puberty were observed in none of the patients of the No CRT arm and in 27·8% and 29·4% respectively in the CRT arm. Delayed puberty was diagnosed in 10·5% of the patients in the No CRT arm vs. 12·5% in the CRT arm. Finally, we have investigated the impact of TBI in first- or second-line treatments on the different endocrine LAE. The observed rate of GH deficiency was 100% in the TBI group ($n = 5$) vs. 31·5% without TBI ($n = 54$), the rate of hypothyroidism was 100% with TBI ($n = 3$) vs. 6·1% without TBI ($n = 33$) and the rate of delayed puberty was 100% with TBI ($n = 2$) vs. 6·1% without TBI ($n = 33$). Similar trends were observed in study 58831 (see Table SI).

Discussion

With dramatic improvements in the survival of childhood ALL patients over the last 50 years, the need for a comprehensive appraisal of their long-term outcome, including the late effects of the treatments, has been increasingly recognized. In this context, the benefit–risk balance for the use of CRT as part of the CNS prophylaxis remained controversial for patients presumed to be at increased risk of CNS relapse. Here, we updated, with very-long-term data, the results of the randomization comparing No CRT *versus* CRT in medium/high-risk childhood ALL patients included in study 58832 (1983–1989) and evaluated the incidence of SN and the rate of LAE by treatment arm.

Patients randomized in the No CRT arm had similar 25-year incidence of any (8·7% vs. 11·9%) and of isolated (6·5% vs. 4·8%) CNS relapse compared to the CRT arm. A recent retrospective meta-analysis evaluated the influence of CRT on the outcome of childhood ALL patients, based on aggregate data from 16,623 ALL children aged 1–18 years and treated in ten collaborative trials. In two trials [DCOG ALL-9 (Veerman *et al.*, 2009) and Total Therapy XV (Pui *et al.*, 2009)], CRT was not part of first-line treatment, while in the eight other studies, CRT was restricted to 2–33% of the patients, considered to be at high risk of CNS relapses. In non-CNS3 patients, there was no benefit for CRT in terms of incidence of any CNS relapse, isolated CNS relapse and survival at five years (Vora *et al.*, 2016). In patients with CNS-3 status, the rates of any and isolated CNS relapse were higher without CRT (16·7% vs. 6·8% and 16·7% vs. 4·3% respectively), with similar five-year mortality rates.

In the initial publication of EORTC studies 58831 and 58832 (Vilmer *et al.*, 2000), including 707 standard- and medium/high-risk patients, the 10-year incidence of any CNS

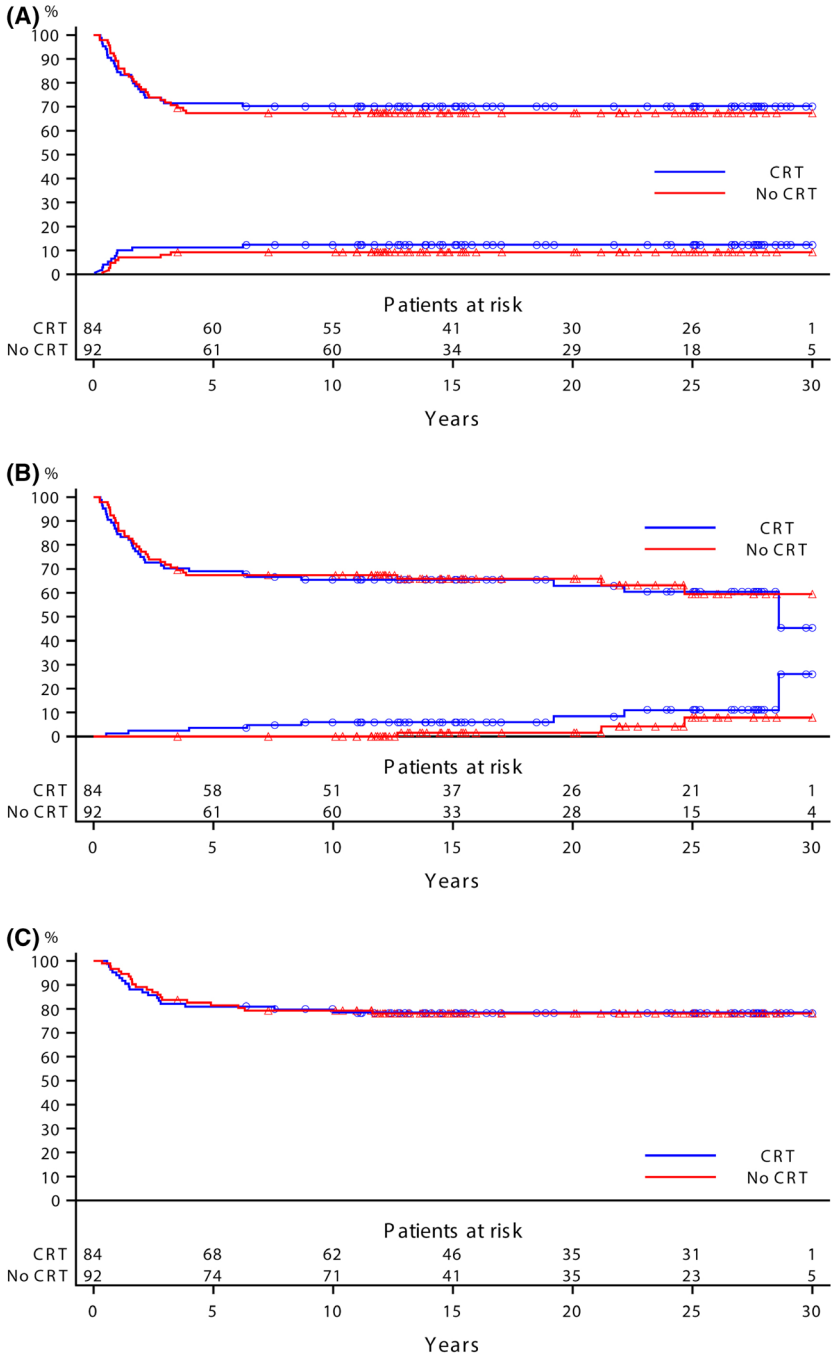


Fig 3. (A) Kaplan–Meier curve of disease-free survival [event: relapse, death in first complete remission (CR1)] and cumulative incidence of any central nervous system (CNS) relapse. (B) Kaplan–Meier curve of event-free survival [event: relapse without second neoplasm (SN), SN in CR1, death in CR1 and without SN] and cumulative incidence of SN in CR1. (C) Kaplan–Meier curve of overall survival by treatment arm [No cranial radiotherapy (CRT) or CRT].

Table II. Characteristics and outcome of patients who developed a second neoplasm.

			First SN						Second SN				
				Treatments as part of ALL therapy					Treatments as part of ALL/SN therapy				
Randomized arm	Sex	Age at diagnosis of ALL	Remission status of ALL	VP16	HSCT/TBI	CRT	Latency since randomization (years)	Type	HSCT/TBI	CRT	Latency since ALL randomization (years)	Type	Survival status and duration since randomization
No CRT	F	5	CR1	–	–	–	12·7	Pleomorphic xanthoastrocytoma	–	–	–	–	Alive at 26·7 years
No CRT	M	2	CR1	–	–	–	21·2	Melanoma	–	–	–	–	Alive at 31·3 years
No CRT	F	11	CR1	–	–	–	24·7	Thyroid carcinoma	–	–	–	–	Alive at 27·0 years
No CRT	F	2	CR2	+	–	+	26·2	Adenocarcinoma of ileum	–	–	27·1	Basal cell carcinoma	Alive at 27·9 years
CRT	M	2	CR1	–	–	–	0·5	Malignant histiocytosis	–	–	–	–	Dead at 0·6 years
CRT	F	10	CR1	–	–	–	1·5	AML	+	–	–	–	Alive at 28·7 years
CRT	M	3	CR1	–	–	–	4·0	AML	+	–	26·6	Meningioma	Alive at 26·8 years
CRT	F	8	CR1	–	–	–	6·4	NHL	–	–	–	–	Alive at 26·8 years
CRT	M	3	CR1	–	–	–	8·7	Thyroid carcinoma	–	–	–	–	Alive at 27·6 years
CRT	M	5	CR1	–	–	–	19·2	Meningioma	–	UKN	–	–	Alive at 19·2 years
CRT	F	11	CR2	–	+	+	20·3	Meningioma	–	–	–	–	Alive at 27·5 years
CRT	F	10	CR1	–	–	–	22·2	Meningioma	–	–	23·2	Meningioma	Alive at 29·1 years
CRT	F	5	CR1	–	–	–	28·6	Meningioma*	–	–	–	–	Alive at 28·9 years

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CR, complete remission; CRT, cranial radiotherapy; HSCT, haematopoietic stem cell transplantation; NHL, non-Hodgkin lymphoma; SN, second neoplasm; TBI, total body irradiation; UKN, unknown.
*Two synchronous meningiomas.

Table III. Distribution of the late adverse effects according to the treatment (EORTC study 58 831 and No CRT vs CRT in EORTC study 58 832).

Type of LAE (CTCAE 4.0, grades 1–4)	EORTC study 58 831* No CRT ($N = 272$) N observed LAE/N available data (%)	EORTC study 58 832† No CRT ($N = 92$) N observed LAE/N available data (%)	EORTC study 58 832† CRT ($N = 84$) N observed LAE/N available data (%)
Leukoencephalopathy	1/61 (1.6)	2/23 (8.7)	5/26 (19.2)
Cognitive disturbance	4/64 (6.3)	3/16 (18.8)	8/19 (42.1)
Seizures	11/101 (10.9)	1/27 (3.7)	4/28 (14.3)
Stroke	1/90 (1.1)	0/26 (0.0)	2/26 (7.7)
GH deficiency	8/88 (9.1)	5/27 (18.5)	17/32 (53.1)
Hypothyroidism	3/61 (4.9)	0/18 (0.0)	5/18 (27.8)
Precocious puberty	2/60 (3.3)	0/18 (0.0)	5/17 (29.4)
Delayed puberty	5/59 (8.5)	2/19 (10.5)	2/16 (12.5)

CRT, cranial radiotherapy; GH, growth hormone; LAE, late adverse effects.

*Methotrexate injections at 0.5 g/m^2 during interval therapy.

†Intermediate-dose methotrexate injections at 2.5 g/m^2 during interval therapy.

relapse was approximately 10%, and was comparable to that of the similar ALL-BFM 83 study (8·7%) (Möricke *et al.*, 2010). In the EORTC study, only 12% received CRT in CR1 whereas in the BFM study, 70% of the patient population had to receive CRT (at age-dependent dose), including the CNS-3 patients (2·9%).

The eight-year incidence of any and isolated CNS relapse progressively decreased in subsequent EORTC studies, despite the omission of CRT for all patients in CR1: 7·6% and 3·6% respectively in study 58881 (1989–1998) (Sirvent *et al.*, 2011), and 3·7% and 1·7% in study 58951 (1998–2008) (Domenech *et al.*, 2014). DCOG and St. Jude also omitted CRT for all patients in their respective ALL-9 (Veerman *et al.*, 2009) and Total Therapy XV (Pui *et al.*, 2009) studies, and reported isolated CNS relapse incidences of 2·6% and 2·7% respectively. In their subsequent ALL-10 study, DCOG administered CRT at 12 Gy in high-risk patients older than three years who were not receiving stem cell transplantation (0·6% of the patients) and reported a five-year isolated CNS relapse incidence of 1·4% (Pieters *et al.*, 2016). In the current Total Therapy XVI, St. Jude omits CRT in all patients but intensifies the systemic CNS prophylaxis (e.g. up to 27 intrathecal injections) for standard/high-risk patients at high risk of CNS relapse [CNS positive, WBC $\geq 100 \times 10^9$/l, T-cell ALL, t(1;19)/E2A-PBX1, presence of Philadelphia chromosome, MLL rearrangement, hypodiploidy <44]. In the current EORTC 58081 study, CRT is not part of the first-line treatment strategy. MTX is infused at the dose of 5 g/m^2, and leucovorin is given at the dose of 12 mg/m^2 at 6-h intervals, from 42 h until 72 h after the start of MTX infusion, or until MTX serum level is $<2 \times 10^{-7}$ mol/l. The use of PEGylated asparaginase and the monitoring of its activity are recommended, since L-asparaginase plays a role in preventing CNS relapses (Sirvent *et al.*, 2011). Patients with CNS-3 status receive dexamethasone during induction or receive a higher cumulative dose of dexamethasone during late intensification, depending on their initial risk group. The number of intrathecal chemotherapy injections ranges from 11 in CNS-negative very low-risk patients to 22 in CNS-3 very high-risk patients.

The 20-year median follow-up enabled us to assess the incidence of SN, since solid SN are known to occur late in follow-up. Interestingly, we found female predominance in patients who developed SN, while the entire patient population showed male predominance. St. Jude reported no sex impact on SN incidence at 20 years from ALL diagnosis, but did observe an increased cumulative incidence of SN at 30 years in females as compared to males (Hijiya *et al.*, 2007). In the general population, neoplasms are less common in females, except for some subtypes, such as thyroid cancers (F/M ratio: 3) or meningiomas (F/M ratio: 2). In our study, basically all meningiomas occurred after 20 years from ALL diagnosis, and the F/M ratio was 1·5. In addition, our results are in line with previous observations documenting a positive association between CRT and SN incidence (Casagranda *et al.*, 2016), particularly for meningiomas (Carret *et al.*, 2006; Renard *et al.*, 2011; Schmiegelow *et al.*, 2013). Also, St. Jude reported an increasing 20-year cumulative incidence of brain tumours with increasing irradiation dose: 1% at 10–21 Gy, 1·7% at >21–30 Gy and 3·2% at >30 Gy (Walter *et al.*, 1998). In our cohort, no patient below the age of two developed SN of the CNS, possibly due to the lower CRT doses administered in younger patients (16 Gy < 1 year, 20 Gy 1– <2 years and 24 Gy ≥ 2 years).

In our study, increased rate of leukoencephalopathy (19·2%) was associated with the use of CRT and of higher doses of MTX, corroborating previous findings. A recent review reported chronic leucoencephalopathy in 18–61% of childhood ALL survivors systematically evaluated by imaging (Partap *et al.*, 2019). Among patients treated in the Total

Therapy XV protocol without CRT and with fve administrations of high-dose MTX and 13 to 25 triple IT, all symptomatic patients and 20·6% of asymptomatic patients had leukoencephalopathy on systematic MRI evaluation, which persisted in 58% of symptomatic and 74% of asymptomatic patients at the end of therapy (Bhojwani *et al.*, 2014). Acute leckoencephalopathy was associated with higher risk for long-term neurocognitive impairment. We observed a higher rate of cognitive disturbance (42·1%) in the CRT arm. Both CRT and, to a lesser extent, chemotherapy are recognized as major risk factors. We observed a fourfold increase in the rate of seizures in the CRT arm (14·3%). Very few data report on the incidence and risk factors of seizures after childhood ALL. Goldsby et al reported an incidence of 20-year seizures of 7% in childhood ALL survivors and did not identify CRT as a risk factor (Goldsby *et al.*, 2010). In our study, the rate of seizures observed in patients treated without CRT and with MTX at 0·5 g/m^2 in study 58831 seemed unexpectedly high in comparison with that of patients treated without CRT and with MTX at 5 g/m^2 in study 58832. Unfortunately, we did not find the aetiology in 8 of the 11 standard-risk patients who developed seizures, making it difficult to draw conclusions regarding the impact of MTX dose on the development of seizures.

A higher proportion of patients randomized in the CRT arm developed endocrine disorders, including GH deficiency (53·1%). This is consistent with previous observations reporting a negative impact of CRT on adult height through GH deficiency, particularly after doses ≥18 Gy (Stubberfield *et al.*, 1995; Melin *et al.*, 1998). The effect of chemotherapy on growth velocity is rather linked to decline in insulin-like growth factor and insulin-like growth factor-binding protein 3 levels during initial and continuation therapy but is usually followed by catch-up growth (Schmiegelow *et al.*, 1999). Hypothyroidism was observed in 27·8% in the CRT arm, and in 0% in the No CRT arm. This latter observation is in line with previous reports indicating normal thyroid function in patients treated with chemotherapy alone (Howard & Pui, 2002). In contrast, the literature is conflicting regarding the impact of CRT. The Childhood Cancer Survivor Study observed patient-reported hypothyroidism in 4% and 6·8% of ALL survivors treated without and with CRT respectively (Chow *et al.*, 2013). Consistently, Steffens *et al.* found no difference in the rate of hypothyroidism based on TSH/T4 levels in patients treated without (6%) and with CRT (14%), but identified TBI as a risk factor (Steffens *et al.*, 2008). Our data also support a strong negative impact of TBI on thyroid function. Finally, we observed an association between CRT and precocious puberty, and between TBI and delayed puberty. This is in line with previous reports suggesting that delayed puberty seems related to primary gonadic dysfunction rather than to hypopituitarism.

In conclusion, our observations, based on very-long-term follow-up, add to the body of evidence that, with proper systemic and intrathecal CNS prophylaxis, CRT could totally be omitted in CR1 without jeopardizing OS while decreasing the long-term adverse events in ALL children. Long-term prospective studies will be needed to evaluate the impact of intensified systemic CNS prophylaxis on the neurocognitive outcome (Jacola *et al.*, 2016) and the health-related quality of life (Vetsch *et al.*, 2018) of ALL survivors and optimal schedules need to be established.

Acknowledgements

The authors thank all the EORTC Children Leukaemia Group members and the clinicians who participated in the studies (see Data S1). We also thank the EORTC HQ Data Management Department members (Nicole Duez, Livia Giurgea, Bart Meulemans, Séraphine Rossi and Gabriel Solbu) for their essential support. We warmly thank Gaetan de Schaetzen, EORTC HQ Project Manager, for his invaluable help in this project and Teresa de Rojas, EORTC CLG Fellow for her help in literature review. Finally, we thank Nancy van Damme and Linda Thibaut (Belgian Cancer Registry), and Pr. Jacqueline Clavel (Registre National des Hémopathies malignes de l'Enfant) for their support in the update of the vital status and of second neoplasms. This work was supported by Fonds Cancer (FOCA) from Belgium and the Kinderkankerfonds (a non-profit childhood cancer foundation under Belgian law).

Author contributions

SS, CPi, YBen and RM designed the study; CPi, YBer, AU, EV, GP, CPa,CPl, NS, RM, MP, PS, AF, FM, RP, CF, CT, PP, JvdWTB, PSR and YBen included patients in the trial and provided clinical data; CPi and CG controlled the quality of the data; SS performed the statistical analysis; SS and CPi interpreted the data and prepared the manuscript; CPi edited the manuscript and all authors critically reviewed the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Distribution of the late endocrine adverse effects according to the study (58831 or 58832), randomized treatment (No CRT *versus* CRT) and whether patients received TBI or not.

Data S1. Participating institutions and investigators.

Appendix S1. 58832 LAE: ITT, ITT & Eligible, PPT – Cumul. Incidence any CNS, DFS, OS.

References

Bhojwani, D., Sabin, N.D., Pei, D., Yang, J.J., Khan, R.B., Panetta, J.C., Krull, K.R., Inaba, H., Rubnitz, J.E., Metzger, M.L., Howard, S.C., Ribeiro, R.C., Cheng, C., Reddick, W.E., Jeha, S., Sandlund, J.T., Evans, W.E., Pui, C.H. & Relling, M.V. (2014) Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology*, **32**, 949–959.

Carret, A.-S., Tabori, U., Crooks, B., Hukin, J., Odame, I., Johnston, D.L., Keene, D.L., Freeman, C. & Bouffet, E.; Canadian Pediatric Brain Tumour Consortium. (2006) Outcome of secondary high-grade glioma in children previously treated for a malignant condition: a study of the Canadian Pediatric Brain Tumour Consortium. *Radiotherapy and Oncology*, **81**, 33–38.

Casagranda, L., Oriol, M., Freycon, F., Frappaz, D., Bertrand, Y., Bergeron, C., Plantaz, D., Stephan, J.L., Freycon, C., Gomez, F., Berger, C. & Trombert-Paviot, B. (2016) Second malignant neoplasm following childhood cancer: A nested case-control study of a recent cohort (1987–2004) from the Childhood Cancer Registry of the Rhône-Alpes region in France. *Pediatric Hematology and Oncology*, **33**, 371–382.

Chow, E.J., Liu, W., Srivastava, K., Leisenring, W.M., Hayashi, R.J., Sklar, C.A., Stovall, M., Robison, L.L. & Baker, K.S. (2013) Differential effects of radiotherapy on growth and endocrine function among acute leukemia survivors: a childhood cancer survivor study report. *Pediatric Blood & Cancer*, **60**, 110–115.

Domenech, C., Suciu, S., De Moerloose, B., Mazingue, F., Plat, G., Ferster, A., Uyttebroeck, A., Sirvent, N., Lutz, P., Yakouben, K., Munzer, M., Röhrlich, P., Plantaz, D., Millot, F., Philippet, P., Dastugue, N., Girard, S., Cavé, H., Benoit, Y. & Bertrand, Y. (2014) Dexamethasone (6 mg/m2/day) and prednisolone (60 mg/m2/day) were equally effective as induction therapy for childhood acute lymphoblastic leukemia in the EORTC CLG 58951 randomized trial. *Haematologica*, **99**, 1220–1227.

Goldsby, R.E., Liu, Q., Nathan, P.C., Bowers, D.C., Yeaton-Massey, A., Raber, S.H., Hill, D., Armstrong, G.T., Yasui, Y., Zeltzer, L., Robison, L.L. & Packer, R.J. (2010) Late-occurring neurologic sequelae in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology*, **28**, 324–331.

Green, D.M., Freeman, A.I., Sather, H.N., Sallan, S.E., Nesbit, M.E., Cassady, J.R., Sinks, L.F., Hammond, D. & Frei, E. (1980) Comparison of three methods of central-nervous-system prophylaxis in childhood acute lymphoblastic leukemia. *Lancet*, **1**, 1398–1402.

Hijiya, N., Hudson, M.M., Lensing, S., Zacher, M., Onciu, M., Behm, F.G., Razzouk, B.I., Ribeiro, R.C., Rubnitz, J.E., Sandlund, J.T., Rivera, G.K., Evans, W.E., Relling, M.V. & Pui, C.-H. (2007) Cumulative Incidence of Secondary Neoplasms as a First Event After Childhood Acute Lymphoblastic Leukemia. *JAMA*, **297**, 1207.

Howard, S.C. & Pui, C.-H. (2002) Endocrine complications in pediatric patients with acute lymphoblastic leukemia. *Blood Reviews*, **16**, 225–243.

Jacola, L.M., Krull, K.R., Pui, C.H., Pei, D., Cheng, C., Reddick, W.E. & Conklin, H.M. (2016) Longitudinal assessment of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on a contemporary chemotherapy protocol. *Journal of Clinical Oncology*, **34**, 1239–1247.

Kalbfleisch, J.D. & Prentice, R.L. (2002) The Statistical Analysis of Failure Time Data, 2nd edn. New York, NY: John Wiley.

Langerman, H., Henze, G., Wulf, M. & Rhiem, H. (1982) Abschatzung der tumorzellmasse bei der akuten lymphoblastischen leukamie im kindesalter: prognostische bedeuting und pratische Anwendung. *Klinische Pädiatrie*, **194**, 209–213.

Melin, A.E., Adan, L., Leverger, G., Souberbielle, J.C., Schaison, G. & Brauner, R. (1998) Growth hormone secretion, puberty and adult height after cranial irradiation with 18 Gy for leukaemia. *European Journal of Pediatrics*, **157**, 703–707.

Möricke, A., Zimmermann, M., Reiter, A., Henze, G., Schrauder, A., Gadner, H., Ludwig, W.D., Ritter, J., Harbott, J., Mann, G., Klingebiel, T., Zintl, F., Niemeyer, C., Kremens, B., Niggli, F., Niethammer, D., Welte, K., Stanulla, M., Odenwald, E., Riehm, H. & Schrappe, M. (2010) Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia*, **24**, 265–284.

Partap, S., Russo, S., Esfahani, B., Yeom, K., Mazewski, C., Embry, L., Wheeler, G., Ullrich, N.J. & Bowers, D.C. (2019) A review of chronic leukoencephalopathy among survivors of childhood cancer. *Pediatric Neurology*, pii: S0887-8994(18)31330-4. https://doi.org/10.1016/j.pediatrneurol.2019.03.006.

Pieters, R., De Groot-Kruseman, H., Van Der Velden, V., Fiocco, M., Van Den Berg, H., De Bont, E., Egeler, R.M., Hoogerbrugge, P., Kaspers, G., Van Der Schoot, E., De Haas, V. & Van Dongen, J. (2016) Successful therapy reduction and intensification for childhood acute lymphoblastic leukemia based on minimal residual disease monitoring: Study ALL10 from the Dutch Childhood Oncology Group. *Journal of Clinical Oncology*, **34**, 2591–2601.

Pui, C.-H., Campana, D., Pei, D., Bowman, W.P., Sandlund, J.T., Kaste, S.C., Ribeiro, R.C., Rubnitz, J.E., Ph, D., Raimondi, S.C., Onciu, M., Coustan-smith, E., Kun, L.E., Jeha, S., Cheng, C., Howard, S.C., Simmons, V., Bayles, A., Metzger, M.L., Boyett, J.M., Leung, W., Handgretinger, R., Downing, J.R., Evans, W.E. & Relling, M.V. (2009) Treating childhood acute lymphoblastic leukemia without cranial irradiation. *The New England Journal of Medicine*, **360**, 2730–2741.

Renard, M., Suciu, S., Bertrand, Y., Uyttebroeck, A., Ferster, A.,van der Werff Ten Bosch, J., Mazingue, F., Plouvier, E., Robert, A., Boutard, P., Millot, F., Munzer, M., Mechinaud, F., Lescoeur, B., Baila, L., Vandecruys, E., Benoit, Y. & Philippet, P.; EORTC Children Leukaemia Group (CLG). (2011) Second neoplasm in children treated in EORTC 58881 trial for acute lymphoblastic malignancies: low incidence of CNS tumours. *Pediatric Blood & Cancer*, **57**, 119–125.

Schmiegelow, M., Hertz, H., Schmiegelow, K., Holm, K. & Müller, J. (1999) Insulin-like growth factor-I and insulin-like growth factor binding protein-3 during maintenance chemotherapy of acute lymphoblastic leukemia in children. *Journal of Pediatric Hematology/Oncology*, **21**, 268–273.

Schmiegelow, K., Levinsen, M.F., Attarbaschi, A., Baruchel, A., Devidas, M., Escherich, G., Gibson, B., Heydrich, C., Horibe, K., Ishida, Y., Liang, D.-C., Locatelli, F., Michel, G., Pieters, R., Piette, C., Pui, C.-H., Raimondi, S., Silverman, L., Stanulla, M., Stark, B.,Winick, N.&Valsecchi, M.G. (2013) Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology*, **31**, 2469–2476.

Sirvent, N., Suciu, S., Rialland, X., Millot, F., Benoit, Y., Plantaz, D., Ferster, A., Robert, A., Lutz, P., Nelken, B., Plouvier, E., Norton, L., Bertrand, Y. & Otten, J. (2011) Prognostic significance of the initial cerebro-spinal fluid (CSF) involvement of children with acute lymphoblastic leukaemia (ALL) treated without cranial irradiation: results of European Organization for Research and Treatment of Cancer (EORTC) Children Leukemia Group study 58881. *European Journal of Cancer*, **47**, 239–247.

Steffens, M., Beauloye, V., Brichard, B., Robert, A., Alexopoulou, O., Vermylen, C. & Maiter, D. (2008) Endocrine and metabolic disorders in young adult survivors of childhood acute lymphoblastic leukaemia (ALL) or non-Hodgkin lymphoma (NHL). *Clinical Endocrinology*, **69**, 819–827.

Stubberfield, T.G., Byrne, G.C. & Jones, T.W. (1995) Growth and growth hormone secretion after treatment for acute lymphoblastic leukemia in childhood. 18-Gy versus 24-Gy cranial irradiation. *Journal of Pediatric Hematology/Oncology*, **17**, 167–171.

Veerman, A.J., Kamps, W.A., van den Berg, H., van den Berg, E., Bökkerink, J.P., Bruin, M.C., van den Heuvel-Eibrink, M.M., Korbijn, C.M., Korthof, E.T., van der Pal, K., Stijnen, T., van Weel Sipman, M.H., van Weerden, J.F., van Wering, E.R. & van der Does-van den Berg, A.; Dutch Childhood Oncology Group. (2009) Dexamethasone-based therapy for childhood acute

lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997–2004). *The Lancet Oncology*, **10**, 957–966.

Vetsch, J., Wakefield, C.E., Robertson, E.G., Trahair, T.N., Mateos, M.K., Grootenhuis, M., Marshall, G.M., Cohn, R.J. & Fardell, J.E. (2018) Health-related quality of life of survivors of childhood acute lymphoblastic leukemia: a systematic review. *Quality of Life Research*, **27**, 1431–1443.

Vilmer, E., Suciu, S., Ferster, A., Bertrand, Y., Cave, H., Thyss, A., Benoit, Y., Dastugue, N., Fournier, M., Souillet, G., Manel, A.-M., Robert, A., Nelken, B., Millot, F., Lutz, P., Rialland, X., Mechinaud, F., Boutard, P., Behar, C., Chantraine, J.-M., Plouvier, E., Laureys, G., Brock, P., Uyttebroeck, A., Margueritte, G., Plantaz, D., Norton, L., Francotte, N., Gyselinck, J., Waterkeyn, C., Solbu, G., Philippe, N. & Otten, J. (2000) Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: A CLCG-EORTC report. *Leukemia*, **14**, 2257–2266.

Vora, A., Andreano, A., Pui, C.-H., Hunger, S.P., Schrappe, M., Moericke, A., Biondi, A., Escherich, G., Silverman, L.B., Goulden, N., Taskinen, M., Pieters, R., Horibe, K., Devidas, M., Locatelli, F. & Valsecchi, M.G. (2016) Influence of cranial radiotherapy on outcome in children with acute lymphoblastic leukemia treated with contemporary therapy. *Journal of Clinical Oncology*, **34**, 919–926.

Walter, A.W., Hancock, M.L., Pui, C.H., Hudson, M.M., Ochs, J.S., Rivera, G.K., Pratt, C.B., Boyett, J.M. & Kun, L.E. (1998) Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. *Journal of Clinical Oncology*, **16**, 3761–3767.