TITLE PAGE

Title:

Fertility status among long-term childhood acute lymphoblastic leukaemia survivors enrolled between 1971 and 1998 in EORTC CLG studies: results of the 58 Late Adverse Effects study

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Running title: Fertility among long-term childhood ALL survivors

ABSTRACT

Study question: What are the fertility outcomes of male and female childhood acute lymphoblastic leukaemia (ALL) long-term survivors?

Summary answer: We observed similar fertility outcomes in both male and female childhood ALL survivors compared to the general population, with the exception of a higher proportion of miscarriages among partners of male survivors.

What is known already: Survival after childhood ALL is currently greater than 90% and fertility impairments are among the main concerns of the long-term survivors. Few studies have focused on the fertility issues within this selected population and the existing data is difficult to interpret due to the different treatment regimens received by the patients, the small sample sizes and the unavailability of control data in many studies.

Study design, size, duration: Childhood ALL patients enrolled in European Organisation for Research and Treatment of Cancer (EORTC) studies between 1971-1998 in France and Belgium, <18 years old at diagnosis, and alive and ≥18 years at follow-up were eligible. Among 1418 eligible survivors, 507 (35.8%) participated (277 females, 230 males). Controls from the general population matched one-to-one by age, province, level of urbanisation and sex could be identified for 503 survivors.

Participants/materials, setting, methods: Survivors and controls were invited to fill out a questionnaire including information about their menstrual cycles (for females), intention to have children, having children, use of medical help to become pregnant and occurrence of negative pregnancy outcomes (birth defect, miscarriage, medical abortion or stillbirth). The results were analysed separately for females and males. The association between age at diagnosis and fertility outcomes, adjusted by age at follow-up, study and country were investigated using logistic regression.

Main results and the role of chance: The median time since diagnosis was 20.1 years and the median age at follow-up 25 years. There were 144 survivors (97 female, 47 male) who wanted to have children. Among these, craniospinal radiotheraphy (CRT) and haematopoietic stem cell transplantation (HSCT) were administered to 18% and 4%, respectively. Of these who tried to have children, 75% of females and 69% of males succeeded, compared with 72% and 61% of the controls, respectively. These differences were not statistically significant (p = 0.73 for females and p = 0.50 for males*).* Overall, fertility outcomes were comparable between survivors and controls, except that a higher proportion of miscarriages occurred in partners of male survivors (28.1% versus 5.9%, p = 0.021). Among female survivors, older age at diagnosis (10-17 years) was associated with a greater risk of pregnancy problems (adjusted OR 5.61, p = 0.046).

Limitations, reasons for caution: The interpretation of the incidence of miscarriage among the partners of male survivors is limited by the lack of data regarding the males' partners and by a possibly higher tendency to recall and disclose fertility issues among male survivors compared to male controls.

Wider implications of the findings: Fertility outcomes were similar in childhood ALL survivors and controls, and the low proportion of patients treated with CRT or HSCT might explain this. Further studies should confirm the higher proportion of miscarriages in partners of male survivors.

Study funding/competing interest(s): This publication was supported by donations from the Fonds Cancer (FOCA) from Belgium and from KU Leuven from Belgium. G.R. has been awarded a fellowship by the EORTC Cancer Research Fund (ECRF). C.P. has been awarded a fellowship by Fonds Cancer (FOCA) from Belgium and the Kinderkankerfonds from Belgium (a non-profit childhood cancer foundation under Belgian law). No competing interests were declared.

Trial registration number: NCT01298388 (clinicaltrials.gov).

Keywords

acute lymphoblastic leukemia / childhood cancer survivors / long term adverse effects / survivorship / infertility / alkylating antineoplastic agents / hematopoietic stem cell transplantation / cranial radiotherapy / miscarriage

Introduction

Survival after childhood acute lymphoblastic leukaemia (ALL) has increased over the last 40 years (Pui *et al.*, 2015; van Dorp *et al.*, 2018). The expected cure rate is currently greater than 90%, and the attention is now focused on the long-term outcome of the survivors. Fertility impairments are among their main concerns, and may affect their psychophysical well-being (Gorman *et al.*, 2015). The treatments for ALL may impair reproductive function, either directly by damaging the testicular germinal epithelium, the ovarian follicular reserve and other reproductive organs, or indirectly by acting on the hypothalamic-pituitary axis (Chemaitilly *et al.*, 2018). The major risk factors in this population include exposure to high doses of alkylating agents (von der Weid, 2008; Thomas-Teinturier *et al.*, 2015), prophylactic craniospinal or cranial radiotherapy (CRT) (Wo and Viswanathan, 2009; Chemaitilly *et al.*, 2015; Green *et al.*, 2017; Piette *et al.*, 2020), total body irradiation (TBI) before haematopoietic stem cell transplantation (HSCT) and testicular irradiation (Bruzzi *et al.*, 2019). In the literature, long-term complications of therapies, including fertility issues, were more frequently examined in reviews articles (Thomson *et al.*, 2002; van Dorp *et al.*, 2018) and studies (Green *et al.*, 2002, 2010; Wasilewski-Masker *et al.*, 2014; Chow *et al.*, 2016; van der Kooi *et al.*, 2017; van Dijk *et al.*, 2020; Sylvest *et al.*, 2021) conducted in mixed cohorts of childhood cancer survivors. In studies focusing on ALL patients, treatment-related fertility deficits were analysed separately in males (Humpl *et al.*, 1999; Byrne *et al.*, 2004a; Green *et al.*, 2017) and females (Byrne *et al.*, 2004b) or in specific populations treated with TBI (Freycon *et al.*, 2019) or CRT (Byrne *et al.*, 2004b; Green *et al.*, 2017). Fertility impairments and family plans were compared with those of ALL survivors' siblings in some reports (Byrne *et al.*, 2004a, 2004b). In general, the existing data is difficult to interpret due to the different treatment regimens received by the patients (Bruzzi *et al.*, 2019), the small sample sizes, and the unavailability of control data in many studies.

The goal of our follow-up study is an overall assessment of fertility status in both male and female childhood ALL and lymphoblastic lymphoma (LBL) survivors, compared to matched controls among the general population. This study is part of the larger European Organisation for Research and Treatment of Cancer (EORTC) Children's Leukemia Group (CLG) 58 Late Adverse Effects (LAE) study (ClinicalTrials.gov Identifier NCT01298388), assessing the long-term outcomes of childhood ALL and LBL survivors (Piette *et al.*, 2018). We will refer to the combined group of ALL and LBL as ALL in the remainder of this manuscript.

Methods

Patient population

Childhood ALL patients enrolled between 2012 and 2017 in the 58LAE study (Piette *et al.*, 2018) were included in our fertility sub-study. Eligible patients for the current study were those treated between 1971 and 1998 and included in the EORTC studies (58741, 58831/2 and 58881) conducted in France and Belgium, <18 years old at diagnosis, and alive and ≥18 years at follow-up.

Treatment protocols

Details regarding studies 58741, 58831/2 and 58881 are reported in Table I and in Supplementary Figure S1. In study 58741, CRT was administered to all patients. Then, studies 58831/2 investigated whether CRT could be omitted with systemic and intrathecal central nervous system (CNS) prophylaxis in CNS-negative patients. Based on these results, CRT was fully omitted in the 58881 study. HSCT was reserved to very high-risk patients enrolled in study 58881 in first remission if a donor was available.

Ethics

At the time of the enrolment in studies 58741, 58831/2 and 58881, informed consent was sought according to local practice of each participating center and in accordance with the Declaration of Helsinki. The EORTC study 58LAE was approved by the Ethical Committees of the participating institutions and informed consent was obtained from all patients, in accordance with the applicable national legislation.

Data collection among the patients

As part of the 58LAE study, the survivors were invited by the participating institutions to fill out the "Questionnaire on long-term outcome after leukemia", derived from the "Life Situation Questionnaire" developed by the EORTC Lymphoma group and including information about their fertility and parenthood situation (Van Der Kaaij *et al.*, 2012). Patients were considered as "lost to follow-up" in case they could not be reached. At least two attempts were made to contact each patient. They were considered as "refusing to take part" in case they clearly stated their refusal by mail or by phone.

Matched controls and data collection among the matched controls group

Two control samples were obtained, one matched and one not matched by the level of education. In the first step, for each survivor a population control was sampled with the same age category (18-19, 20-21, … 38-39, 40-44, 45-52 years), province, level of urbanisation (urban versus rural area) and sex. The controls were provided with a computer- and mobile-device-based survey through an anonymous link, so that the General Data Protection Regulation was guaranteed. The questionnaire they filled in ("Global questionnaire for general population") was identical to the one completed by the survivors (except for questions related to ALL). One to one matched controls could be identified for 503 survivors.

Using this data, 348 survivors could be matched one to one by region (Flanders versus Wallonia versus Brussels versus France), level of urbanisation, sex and level of education (no secondary school diploma versus secondary school diploma and no university degree versus university degree) with the population controls. In case several of the 503 controls matched one survivor, one control was randomly selected to be used in the analysis. In the second step, in order to obtain a sample of controls matched by the level of education, controls matched one to one by region, level of urbanisation, sex and the level of education were searched for the remaining 155 cancer survivors.

Fertility outcomes

The following outcomes were measured both in cancer survivors and controls: ever trying to have children, having children among those survivors who tried to have children, using medical help to become a parent among those who tried to have children, the use of specific reproductive technologies (induction of ovulation, intrauterine insemination, in-vitro fertilisation, intra-cytoplasmic sperm injection) among females who tried to have children, having a child without the use of medical help among females who tried to have children, negative pregnancy outcome among females who had ever been pregnant and males whose partner had ever been pregnant (defined as any history of miscarriage, medical abortion, stillbirth or birth defects), current status of menstrual cycles among females between 18 and 45 years of age, and ever having menstrual cycles among females. In addition, discontinuation of menstrual cycles during ALL treatment among females who had menstrual cycles before diagnosis and the return of menstrual cycles after ALL treatment among females whose menstrual cycles discontinued during the treatment were assessed.

Statistical analysis

The analysis was carried out using SAS version 9.4. All tests were performed at a two-sided significance level of 0.05. We described all binary outcomes separately for males and females. The confidence intervals were estimated using the exact method of Clopper and Pearson (Clopper and Pearson, 1934). The exact Fisher test was used to compare the distribution of categorical outcomes between patients and controls. In the main analysis, the controls were matched by age, province, level of urbanisation and sex. In order to study the robustness of our findings, we compared in a sensitivity analysis survivors to controls matched by region, level of urbanisation, sex and the level of education, given that the level of education could impact outcomes related to fertility, like the age of having children.

Logistic regression was used to investigate the associations between the age at diagnosis (10-17 versus < 10) and menstruation status prior to the diagnosis and fertility of females. All models included the following covariates: country (France versus Belgium), age at follow-up, and protocol. To allow for non-linear effects, age at follow-up was modelled using restricted cubic splines with four knots located at the 5^{th}, 25^{th}, 75^{th} and 95^{th} percentiles (Harrell, 2001).

Results

Patient population

Among 1418 survivors eligible for participation in the current study, 507 patients (35.8%) provided information about fertility status and were included in the fertility sub-project: 25 in the 58741, 109 in the 58831/2 and 373 in the 58881 study, of which 277 were females and 230 were males (Supplementary Figure S2). The distribution of disease characteristics was similar between respondents, patients lost to follow-up, and patients who refused to participate (Supplementary Table SI), providing no evidence of a selection bias. There were slightly more

females in the subgroup of respondents. Of note, the survivors had a high level of education. In fact, 55% of those who were ≥25 years had a university degree. The median time between the diagnosis and the fertility evaluation was 20.1 years (range 12.9-41.5). The median age at follow-up was 25.4 years among females (range 18.1-52.8) and 25.2 years among males (range: 18.3-51.9).

A total of 144 survivors (97 females, 47 males) ever tried to become pregnant or to father a child. Among these, 120 (80 females, 40 males) were married or lived with a partner at the time of the survey. Of the 144 patients, 41 were 10-17 years old at diagnosis, 26 patients (18%) had received CRT and 6 patients (4%) had received HSCT, while 18 patients (13%) had relapsed and, among these, two males had a gonadal relapse (Table II).

Matched controls

We identified 503 population controls matched one to one with survivors by age, province, level of urbanisation and sex. Due to concerns about data quality, 12 controls were excluded from the analysis. The final sample used in the analysis included 491 survivors and 491 one to one matched controls (275 females and 216 males in each group).

The characteristics of controls compared to the ones of survivors are illustrated in Supplementary Table SII.

Among controls, 122 (73 females, 49 males) expressed the wish to have children. Among these, 98 (58 females, 40 males) were married or lived with a partner at the time of the survey.

Data for 480 controls (262 females and 218 males) matched one to one by region, level of urbanisation, sex and the level of education was available for a sensitivity analysis correcting for this indicator of the socioeconomic status.

Fertility of females

The menstruation history of female survivors is summarised in Supplementary Table SIII.

A total of 97 (36%) female survivors and 73 (31%) female controls matched by province, level of urbanisation, age and sex tried to have children. Among them, respectively 75% and 72% succeeded (Table III). The use of reproductive technologies was reported by 12% of the female survivors and 19% of the controls who tried to become pregnant. However 75% female survivors and 64% female controls had at least one child with no use of reproductive technologies. One or more negative pregnancy outcomes (birth defects, miscarriages, medical abortions or stillbirths) were found in 22% of the female survivors and in 30% of the controls, with a percentage of miscarriages of 19% among the survivors and 16% among the controls (Table III). In a sensitivity analysis matched by the level of education, the fertility outcomes of female survivors were again comparable to those of controls (data not shown).

Among female survivors who have been pregnant, older age at diagnosis (10-17 versus <10 years old) was associated with a greater risk of pregnancy problems (32% versus 19%; adjusted OR 5.61, 95% CI: 1.03-30.6) (Figure 1). The results were similar for the association between the presence of menstrual cycles before diagnosis and the risk of negative pregnancy outcomes (31% of patients with negative pregnancy outcomes for those with menstrual cycles versus 21% for those without, adjusted OR 4.41, 95% CI: 0.66-29.42). Details about fertility of female survivors who had menstrual cycles at the time of the diagnosis are provided in Supplementary Table SIV. Regarding the chances of not having attempted pregnacy or not having children, there were no significant differences between patients diagnosed before or after 10 years of age (Figure 1) or between those with or without menstrual cycles at diagnosis (data not shown).

Fertility of males

Comparing 216 male survivors for whom a control matched by province, level of urbanisation, age and sex was available to controls, 22% of survivors and 23% of controls attempted to have children and 69% and 61%, respectively, succeeded (Table IV). Among those who tried to have children, 9% of the survivors and 14% of the controls used medical help for attempting pregnancy. One or more negative pregnancy outcomes was reported by 34% of the partners of the male survivors and in 21% of the partners of the male controls. A statistically significant difference between the partners of survivors and controls was found in the proportion of miscarriages (28% versus 6%, respectively, $p = 0.021$) (Table IV). In a sensitivity analysis matched by the level of education, the results were similar (data not shown).

Discussion

Overall, our results showed comparable fertility outcomes between childhood ALL survivors and controls, except for a higher proportion of miscarriage among partners of male ALL survivors and a greater risk of pregnancy problems among female ALL survivors who were older than 10 years at diagnosis.

In the literature, few studies have focused on the fertility issues within this selected population. Overall, they report good fertility outcomes except for some treatment subgroups.

The negative impact of HSCT on fertility is well recognised, both with TBI and high-dose chemotherapy (Borgmann-Staudt *et al.*, 2012). In our study, only 4% of the survivors who wanted to have children underwent HSCT. This percentage is similar to the proportion of childhood ALL patients who received HSCT in first complete remission in current EORTC protocols (5.2% in EORTC study 58951 (Domenech *et al.*, 2014)). With the recent

implementation of the chimeric antigen receptor (CAR)-T cells in front-line treatments, it is expected that the proportion of patients treated with HSCT could decrease.

The impact of CRT, which was a standard treatment for ALL patients in the past, has been emphasised in several studies. Byrne et al. conducted two studies in 213 male (Byrne *et al.*, 2004a) and 182 female (Byrne *et al.*, 2004b) childhood ALL survivors diagnosed between 1970 and 1987. Among males, patients treated before the age of 10 with CRT at 24 Gy had a significant lower fertility compared to controls (RR=0.09, 95% CI 0.01-0.82). In females, a lower fertility was observed in patients treated with CRT at any dose around the time of the menarche, as compared to controls (RR = 0.27, 95% CI 0.09-0.82). These results are consistent with those of another evaluation of 280 childhood ALL survivors treated between 1962 and 1985 (Nygaard *et al.*, 1991). Overall, the fertility of females up to the age of 23 was similar that of controls (21.1% vs 29.5%, respectively), but fertility of females treated with CRT was significantly reduced compared to females treated without CRT (RR=0.39, 95% CI 0.15-1.00). Finally, a German nationwide survey was conducted among 1476 childhood leukaemia survivors treated between 1980 and 2004, of whom 89% were ALL survivors (Zynda *et al.*, 2012). A total of 93.3% of female and 89.3% of male survivors (mean age 25.7 years, range 19-43 years) reported a general wish to have their own children, which was comparable to the general population, although they reported parenthood less frequently (21.9% vs 43% and 62.2% vs 77% respectively in the age groups 25-34 and 35-44 years, respectively). This could partly be explained by the high proportion of ALL patients treated with CRT (61% received CRT versus 18% in our study). Furthermore, as in our study, the survivors received higher levels of education compared to the general population, and this could also explain the lower incidence of parenthood. The pathogenesis of CRT-altered fertility is probably multifactorial. Quigley et al. reported that GnRH deficiency did not occur after prophylactic CRT as part of the treatment of childhood ALL (Quigley *et al.*, 1989), while Bath et al. reported that pre-

pubertal females treated with low-dose CRT (18-24 Gy), although achieving the menarche, presented subtle ovulatory disorders (Bath *et al.*, 2001). Reproduction depends on a complex of biological and psychosocial factors, and therefore the neuropsychological effects of CRT could also affect behavioural patterns and thus influence sexual life and reproduction.

Looking at the pregnancy outcomes, we found a statistically significant difference between survivors and controls in the proportion of miscarriages (28% versus 6%, respectively) only among the partners of male survivors. This finding might be ascribed to germline mutations induced by chemotherapy, leading to embryonic lethality (Anderson *et al.*, 1995; Gutierrez and Hwang, 2017). However we also noticed that the proportion of the female controls who had a miscarriage was higher (16%) than that of the partners of the male controls (6%). In the German nationwide survey cited above, there were similar percentages of miscarriages compared to the general population, both for male and female survivors (Zynda *et al.*, 2012). The Childhood Cancer Survivor Study compared the pregnancy outcomes of partners of the male childhood cancer survivors treated between 1970 and 1986, to those of the partners of the male siblings (Green *et al.*, 2003). Among 509 pregnancies, they found similar proportions of miscarriage (RR=1.08, 95% CI 0.77-1.52). Overall, the rate of miscarriage was not increased by testis, cranial or craniospinal irradiation and by various doses of cyclophosphamide. Our finding should definitely be investigated in other cohorts of childhood ALL survivors.

Finally, we found greater risk of pregnancy problems in female ALL survivors older than 10 years at diagnosis. These results suggest that pre-pubertal, hypogonadotropic female patients may have a better prognosis regarding gonadotoxicity, compared to the post-pubertal, normogonadotropic patients (Chemaitilly *et al.*, 2006; Green *et al.*, 2009).

Fertility preservation in these patients deserves some considerations. According to the recent PanCareLIFE Consortium guidelines and based on the treatments causing a risk of infertility and mostly used in current childhood ALL protocols (i.e. HSCT, low-dose alkylating agents -

cyclophosphamide-equivalent dose < 6000-8000 mg/m² - and CRT), we would suggest the following recommendations. (1) In post-pubertal female ALL patients, oocyte or embryo cryopreservation is strongly recommended before HSCT and moderately recommended, in patients at high risk of recurrence, before low-dose alkylating agents and before CRT. (2) In pre-pubertal female ALL patients, ovarian tissue cryopreservation is moderately recommended before HSCT (Renée L Mulder et al., 2021a). (3) In pubertal or post-pubertal male ALL patients, sperm cryopreservation (including via electro-ejaculation or testicular spermatozoa extraction) is strongly recommended before HSCT or testicular radiotherapy, low-dose alkylating agents and CRT. (4) In pre-pubertal male ALL patients, testicular tissue cryopreservation is moderately recommended before HSCT and testicular radiotherapy (Renée L Mulder et al., 2021b). In the light of current knowledge, we would encourage physicians to follow these recommendations that balance the harms and the benefits of fertility preservation in this population, and tailor them to the needs of the individual patient.

The major strength of our study is the availability of the control population matched one to one by demographic characteristics. This allowed us to avoid the influence of multiple confounding variables. Moreover, the use of a questionnaire allowed the respondents to feel comfortable in replying to sensitive questions as compared to a telephone interview. In addition, the study included a relatively large sample of survivors of the same childhood malignancy. Furthermore, by performing the analyses separately in males and females, we could obtain a full picture of the fertility status in ALL survivors. One limitation is the lack of assessment of the relative contribution of each individual therapy (alkylating agents, CRT, HSCT) due to insufficient number of patients receiving these particular treatments (Table I). We also noticed that a high percentage of both female and male controls resorted using reproductive technologies, and we cannot exclude that controls who agreed to participate in our study were motivated to take part as they had fertility issues. Moreover, the interpretation of the incidence of miscarriage among

the partners of male survivors is limited by the lack of data regarding the males' partners (age, health status, etc.) and by a possibly higher tendency to report health issues in general, and fertility issues in particular, in male survivors compared to male controls. Finally, our study does not include a clinical and a laboratory assessment of fertility status (i.e. fertility parameters such as follicle-stimulating hormone (FSH), estradiol, progesterone, anti-Müllerian hormone (AMH), antral follicle count (AFC)).

Our study observed similar fertility outcomes for both male and female childhood ALL survivors as compared to matched controls, with the exception of a higher proportion of miscarriage among partners of male survivors. These encouraging results could be explained by the low proportion of patients treated with CRT in our study population. The higher proportion of miscarriage in partners of male survivors could possibly be related to germline mutations induced by chemotherapy and should be further investigated. In the future, it would be interesting to conduct similar follow-up studies in patients treated with the modern standard of care CRT-free treatment or reduced-intensity HSCT conditioning (Fujino *et al.*, 2019). From this perspective, we would recommend monitoring ALL survivors in dedicated multidisciplinary clinics that relate to research programs, ensuring a comprehensive assessment of their fertility status, including laboratory parameters.

DATA AVAILABILITY

According to the EORTC Data Sharing policies, data are available under specific conditions (please refer to https://www.eortc.org/data-sharing/).

AUTHORS' ROLES

G.R. designed the study, helped with data interpretation and wrote the original manuscript. M.K. and S.S. carried out the statistical analyses, helped with data interpretation and wrote the original manuscript. E.V., G.P., A.U., C.Pa., M.B., M-F. D., P.S., O.M., C.Pl., A.F., C.F., F.M., J.v.d.W.t.B., C.C., R.P., P.R. helped with data acquisition. T.d.R. helped with data interpretation. G.d.S. coordinated the study. Y.B. designed the study and helped with data acquisition. C.Pi. designed and coordinated the study, helped with data acquisition and interpretation, and wrote the original manuscript. All authors critically reviewed and approved the final version.

ACKNOWLEDGMENTS

The authors thank all the EORTC CLG members and the clinicians who participated in the studies. We also thank the EORTC HQ Data Management Department members (Livia Giurgea, Bart Meulemans, Séraphine Rossi, Nicole Duez and Gabriel Solbu) for their essential support. We thank the EORTC Lymphoma Group and Pr. Michel Henry-Amar who authorised us to adapt the "Life Situation Questionnaire" for our project. Finally, we thank Nancy van Damme, 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 secondary neoplasms.

FUNDING

This publication was supported by donations from the Fonds Cancer (FOCA) from Belgium and from KU Leuven from Belgium. G.R. has been awarded a fellowship by the EORTC Cancer Research Fund (ECRF). C.Pi. has been awarded a fellowship by Fonds Cancer (FOCA) from

370 Belgium and the Kinderkankerfonds from Belgium (a non-profit childhood cancer foundation
371 under Belgian law).

372 **CONFLICT OF INTEREST**

373 None declared.

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FIGURE LEGENDS

Figure 1. Associations between age at diagnosis and fertility outcomes among female survivors. Odds ratio (OR) indicates comparison between those diagnosed at 10 years or older compared to those diagnosed before 10 year of age.

TABLES

Table I. Main characteristics of the first-line treatments according to the EORTC protocols.

Table II. Descriptive statistics by sex of the entire study population and among the survivors who wanted to have children.

Table III. Fertility outcomes among female survivors compared to population controls.

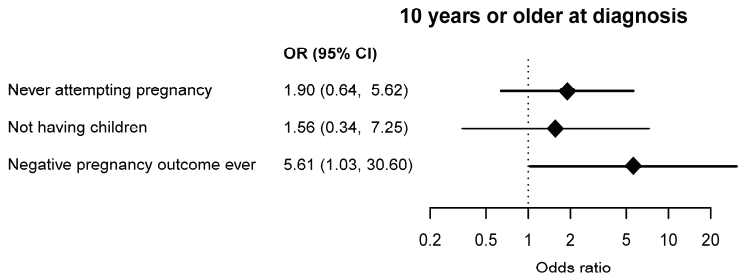
Table IV. Fertility outcomes among male survivors compared to population controls.

SUPPLEMENTARY FIGURES LEGENDS

Supplementary Figure S1. Details regarding the treatments administered in the EORTC study 58741 (a), 58831/2 (b) and 58881 (c) respectively.

Supplementary Figure S2. Patient flow chart.

Figure I. Associations between age at diagnosis and fertility outcomes among female survivors.



Estimated odds ratios (OR) and the 95% confidence interval (CI) from the logistic regression models are provided. For each endpoint, a separate model was fitted adjusted for protocol, country, and age at follow-up. All females (N=274) with available data were included in the models for the outcome 'Never attempting pregnancy'. Females who wanted to have children with available data (N=95) were included in the model for 'Not having children'. Females who had ever been pregnant with available data (N=85) were included in the model for 'Negative pregnancy outcome ever'.

Table I. Main characteristics of the first-line treatments according to the EORTC protocols.

EORTC study	Treatment period	Total cumulative dose of alkylating agents	CRT no/yes (dose)	HSCT no/yes
58741	1971-1978	No vs. 3.92 g/m^2 CPM[a]	Yes (25 Gy)	No
58831[b]	1983-1989	No vs. 2 g/m^2 CPM[a]	No	No
58832[c]:	1983-1989	3 g/m^2 CPM	No vs yes[a] (16, 20 or 24 Gy[d])	No
58881	1989-1998	*Low/intermediate-risk patients:* 3 g/m^2 CPM *High-risk patients:* 2 g/m^2 CPM and 4 g/m^2 IFOS	No	In very high-risk patients in first remission, if a donor was available

[a]Randomised question, [b]Standard-risk patients, [c]Medium and High-risk patients, [d]Dose according to age: 16 Gy (< 1 year), 20 Gy (1-< 2 years), 24 Gy (≥ 2 years). Abbreviations: ALL: acute lymphoblastic leukaemia, CPM: cyclophosphamide, CRT: cranial radiotherapy, HSCT: haematopoietic stem cell transplantation, IFOS: ifosfamide, LBL: lymphoblastic lymphoma

Table II. Descriptive statistics by sex of the entire study population and among the survivors who wanted to have children.

	All Survivors		Survivors who wanted children	
	Females (N=277)	Males (N=230)	Females (N=97)	Males (N=47)
	N (%)	N (%)	N (%)	N (%)
EORTC study				
58741	14 (5.1)	11 (4.8)	9 (9.3)	5 (10.6)
58831	65 (23.5)	44 (19.1)	33 (34.0)	17 (36.2)
58881	198 (71.5)	175 (76.1)	55 (56.7)	25 (53.2)
Age at diagnosis, years				
<10	240 (86.6)	197 (85.7)	73 (75.3)	30 (63.8)
10-17	37 (13.4)	33 (14.3)	24 (24.7)	17 (36.2)
Country				
Belgium	139 (50.2)	97 (42.2)	51 (52.6)	18 (38.3)
France	138 (49.8)	133 (57.8)	46 (47.4)	29 (61.7)
Disease				
ALL	271 (97.8)	227 (98.7)	95 (97.9)	45 (95.7)
LBL	5 (1.8)	3 (1.3)	2 (2.1)	2 (4.3)
missing	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
WBC at diagnosis, x 10□/l				
<25	205 (74.0)	157 (68.3)	71 (73.2)	34 (72.3)
25 - <50	26 (9.4)	33 (14.3)	10 (10.3)	4 (8.5)
≥50	46 (16.6)	40 (17.4)	16 (16.5)	9 (19.1)
Cranial radiotherapy	34 (12.3)	27 (11.7)	16 (16.5)	10 (21.3)
HSCT performed	14 (5.1)	14 (6.1)	4 (4.1)	2 (4.3)
Any relapse	35 (12.6)	32 (13.9)	11 (11.3)	7 (14.9)
CNS relapse	11 (4.0)	10 (4.3)	2 (2.1)	1 (2.1)
Gonadal relapse		6 (2.6)		2 (4.3)
Age at follow-up, years				
18-24	131 (47.3)	110 (47.8)	15 (15.5)	2 (4.3)
25-34	115 (41.5)	105 (45.7)	63 (64.9)	37 (78.7)
35 or older	31 (11.2)	15 (6.5)	19 (19.6)	8 (17.0)
Level of education at follow-up				
No secondary school diploma	8 (2.9)	12 (5.2)	0 (0.0)	2 (4.3)
Secondary school diploma, no university degree	123 (44.4)	97 (42.2)	48 (49.5)	21 (44.7)
University degree	140 (50.5)	119 (51.7)	48 (49.5)	23 (48.9)
Missing	6 (2.2)	2 (0.9)	1 (1.0)	1 (2.1)
Being married or living with a partner				
No	163 (58.8)	149 (64.8)	17 (17.5)	7 (14.9)
Yes	111 (40.1)	80 (34.8)	80 (82.5)	40 (85.1)
Missing	3 (1.1)	1 (0.4)	0 (0.0)	0 (0.0)

Abbreviations: ALL: acute lymphoblastic leukaemia, CNS: Central Nervous System, HSCT: haematopoietic stem cell transplantation, NCI: National Cancer Institute, LBL: Lymphoblastic Lymphoma, WBC: White Blood Cells.

Table III. Fertility outcomes among female survivors compared to population controls.

	Survivors		Controls		
Endpoint	N / N with available information	% (95% CI)	N / N with available information	% (95% CI)	P-value
All matched females (275* survivors and 275 controls)					
Ever trying to become pregnant	97 / 272	35.7 (30.0 - 41.7)	73 / 238	30.7 (24.9 - 37.0)	0.26
Females who tried to become pregnant (97 survivors and 73 controls)					
Having children	71 / 95	74.7 (64.8 - 83.1)	52 / 72	72.2 (60.4 - 82.1)	0.73
Using medical help to become pregnant	11 / 95	11.6 (5.9 - 19.8)	14 / 73	19.2 (10.9 - 30.1)	0.19
Induction of ovulation ever	4 / 93	4.3 (1.2 - 10.6)	6 / 73	8.2 (3.1 - 17.0)	0.34
IUI ever	1/ 93	1.1 (0.0 - 5.8)	6 / 73	8.2 (3.1 - 17.0)	0.044
IVF ever	2 / 93	2.2 (0.3 - 7.6)	4 / 73	5.5 (1.5 - 13.4)	0.41
ICSI ever	3 / 93	3.2 (0.7 - 9.1)	3 / 73	4.1 (0.9 - 11.5)	1.0
Ever having a child with no use of reproductive technologies	70 / 94	74.5 (64.4 - 82.9)	46 / 72	63.9 (51.7 - 74.9)	0.17
Females who had ever been pregnant (86 survivors and 62 controls)					
1 or more birth defects, miscarriages, medical abortions or stillbirths	19 / 85	22.4 (14.0 - 32.7)	18 / 61	29.5 (18.5 - 42.6)	0.34
Birth defect ever	1 / 85	1.2 (0.0 - 6.4)	2 / 61	3.3 (0.4 - 11.3)	0.57
Miscarriage ever	16 / 85	18.8 (11.2 - 28.8)	10 / 61	16.4 (8.2 - 28.1)	0.83
Medical abortion ever	3 / 85	3.5 (0.7 - 10.0)	6 / 61	9.8 (3.7 - 20.2)	0.17
Stillbirth ever	0 / 85	0.0 (0.0-4.2)	2 / 61	3.3 (0.4 - 11.3)	0.17

* For 2 female survivors, no population control was identified. Both of them had never tried to become pregnant.

Population controls were matched by province, level of urbanization, age, and sex.

Abbreviations: ICSI: intracytoplasmic sperm injection, IUI: intrauterine insemination, IVF: In Vitro Fertilization.

Table IV. Fertility outcomes among male survivors compared to population controls.

	Survivors		Controls		
Endpoint	N / N with available information	% (95% CI)	N / N with available information	% (95% CI)	P-value
All matched males (216* survivors and 216 controls)					
Ever trying to have children	46 / 211	21.8 (16.4 - 28.0)	49 / 216	22.7 (17.3 - 28.9)	0.91
Males who tried to have children (46 survivors and 49 controls)					
Having children	27 / 39	69.2 (52.4 - 83.0)	30 / 49	61.2 (46.2 - 74.8)	0.50
Using medical help to make the partner pregnant	4 / 45	8.9 (2.5 - 21.2)	7 / 49	14.3 (5.9 - 27.2)	0.53
Males who had ever made their partner pregnant (33 survivors and 34 controls)					
1 or more birth defects, miscarriages, medical abortions or stillbirths	11 / 32	34.4 (18.6 - 53.2)	7 / 34	20.6 (8.7 - 37.9)	0.27
Birth defect ever	2 / 32	6.3 (0.8 - 20.8)	2 / 34	5.9 (0.7 - 19.7)	1.0
Miscarriage ever	9 / 32	28.1 (13.7 - 46.7)	2 / 34	5.9 (0.7 - 19.7)	0.021
Medical abortion ever	2 / 32	6.3 (0.8 - 20.8)	6 / 34	17.6 (6.8 - 34.5)	0.26
Stillbirth ever	0 / 32	0 (0.0 – 10.9)	0 / 34	0 (0.0 – 10.3)	1.0

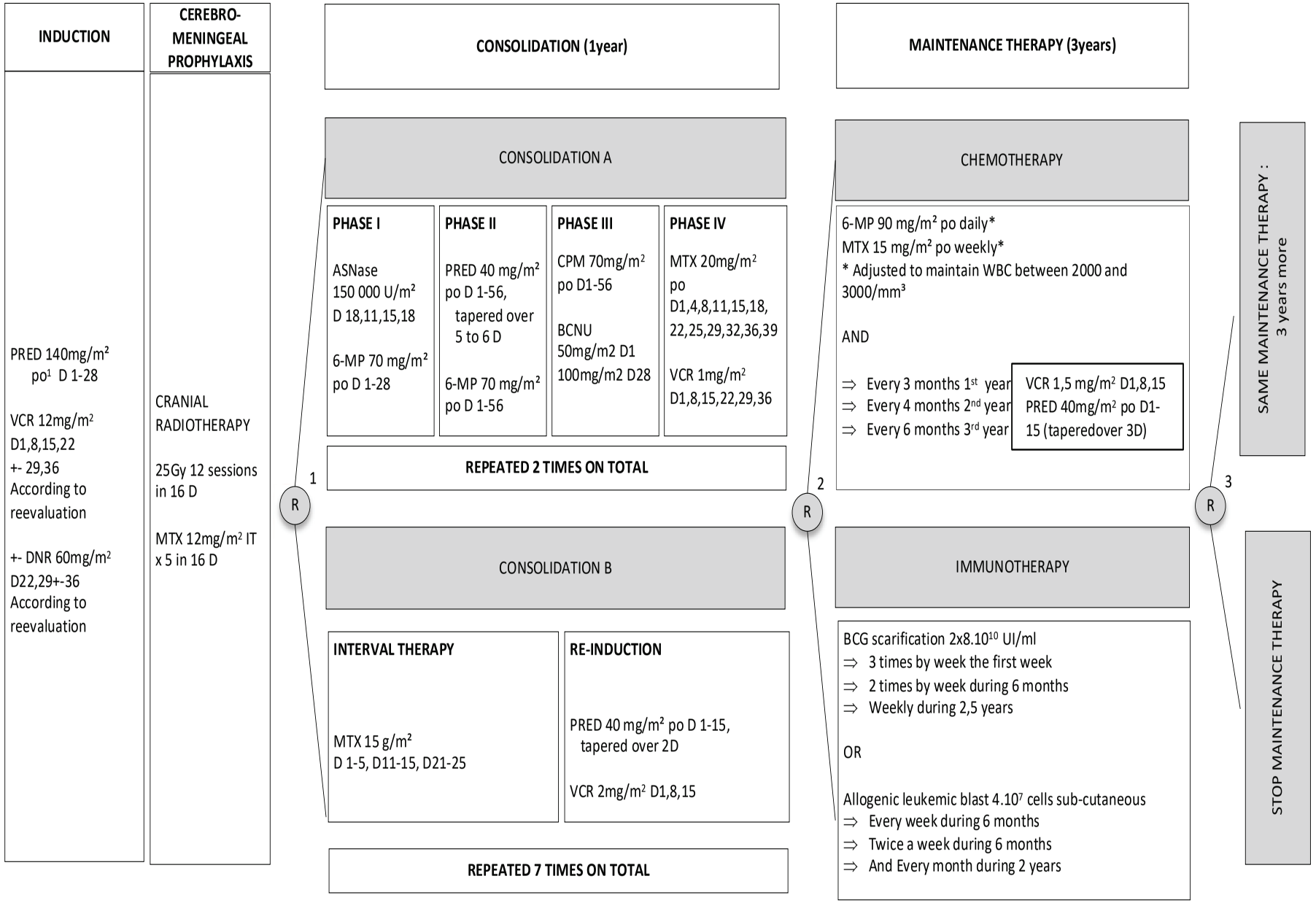
* For 14 male survivors, no population control was identified.

Population controls were matched by province, level of urbanization, age, and sex.

Supplementary Table S X. Fertility outcomes among females with menstrual cycles before the diagnosis.

Endpoint	N (%)
Females with menstrual cycles before the diagnosis (N=21)	
Ever trying to become pregnant	15 (71.4)
Females with menstrual cycles before the diagnosis who tried to become pregnant (N=15)	
Having children	11 (73.3)
Using medical help to become pregnant	2 (14.3)
Females with menstrual cycles before the diagnosis who had ever been pregnant (N=13)	
1 or more birth defects, miscarriages, medical abortions or stillbirths	4 (30.8)
Birth defect ever	1 (7.7)
Miscarriage ever	4 (30.8)
Medical abortion ever	0 (0)
Stillbirth ever	0 (0)

EORTC study 58741

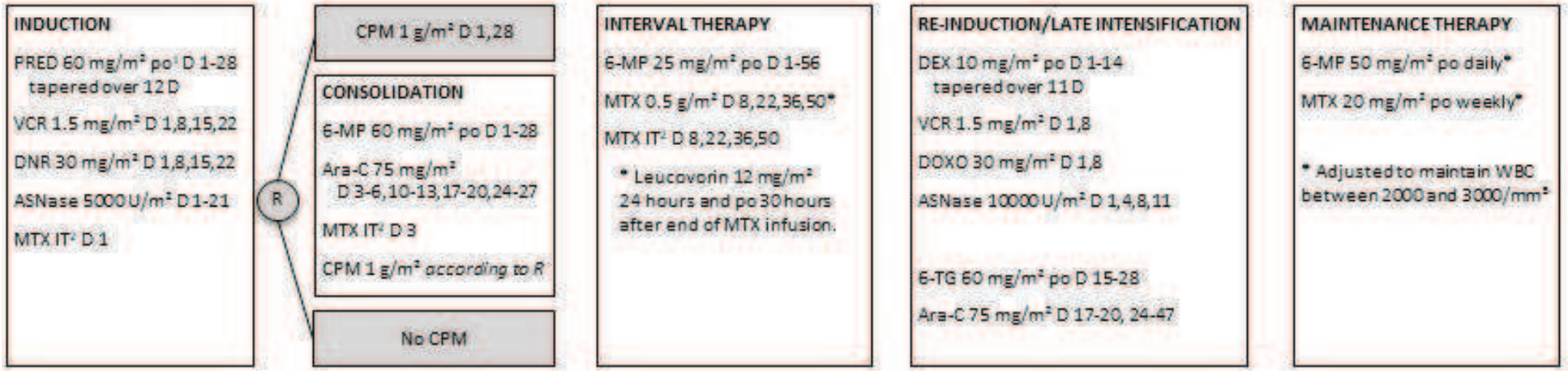


Notes:

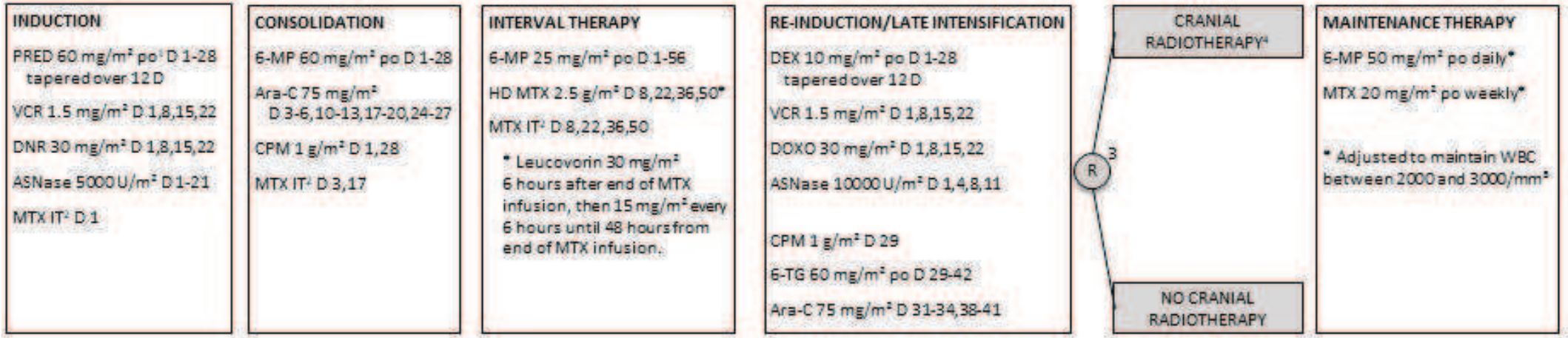
[1] per oral (when not specified, administration is intravenous)

Abbreviations: ASNase: asparaginase, BCNU : Carmustine, CPM: cyclophosphamide, DNR: daunorubicin, 6-MP: 6-mercaptopurine, MTX: methotrexate, PRED: prednisone, R: randomization, VCR: vincristine

EORTC study 58831: standard risk patients (RF<1.2) in CR at the end of induction



EORTC study 58832: medium risk patients (RF 1.2-1.69), high risk patients (RF≥1.7), and standard risk patients (RF<1.2) not in CR at the end of induction



Notes:

[1] Per oral (when not specified, administration is intravenous)

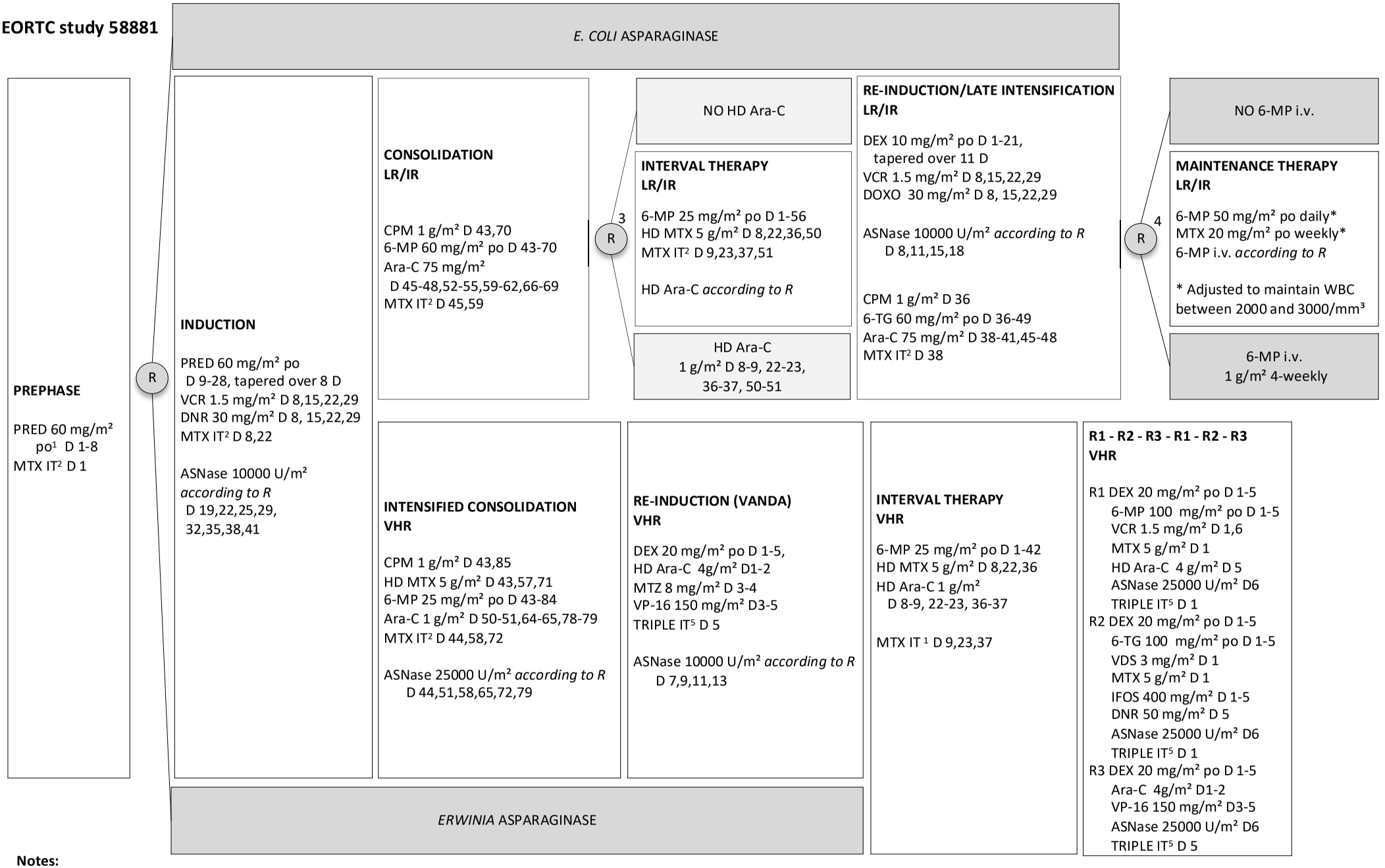
[2] Intrathecal at the dose of 6 mg < 1 year, 8 mg 1-< 2 year, 10 mg 2-<3 year, 12 mg ≥ 3 year

[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

EORTC study 58881



Notes:

[1] per oral (when not specified, administration is intravenous)

[2] intrathecal at the dose of 6 mg < 1 yr, 8 mg 1-< 2 yr, 10 mg 2-<3 yr, 12 mg ≥ 3 yr

[3] IR patients in CR

[4] LR and IR patients in CR

[5] intrathecal at the dose of: MTX: 6 mg < 1 yr, 8 mg 1-< 2 yr, 10 mg 2-<3 yr, 12 mg ≥ 3 yr; Ara-C: 16 mg < 1 yr, 20 mg 1-< 2 yr, 26 mg 2-<3 yr, 30 mg ≥ 3 yr; Prednisone: 4 mg < 1 yr, 6 mg 1-< 2 yr, 8 mg 2-<3 yr, 10 mg ≥ 3 yr

Abbreviations: Ara-C: cytarabine, ASNase: asparaginase, CPM: cyclophosphamide, DEX: dexamethasone, DNR: daunorubicin, DOXO: doxorubicin, HD: high-dose, IFOS: ifosfamide, IR: increased risk, LR: low risk, 6-MP: 6-mercaptopurine, MTX: methotrexate, MTZ: mitoxantrone, PRED: prednisone, R: randomization, 6-TG: 6-thioguanine, VCR: vincristine, VDS: vindesine, VHR: very high risk

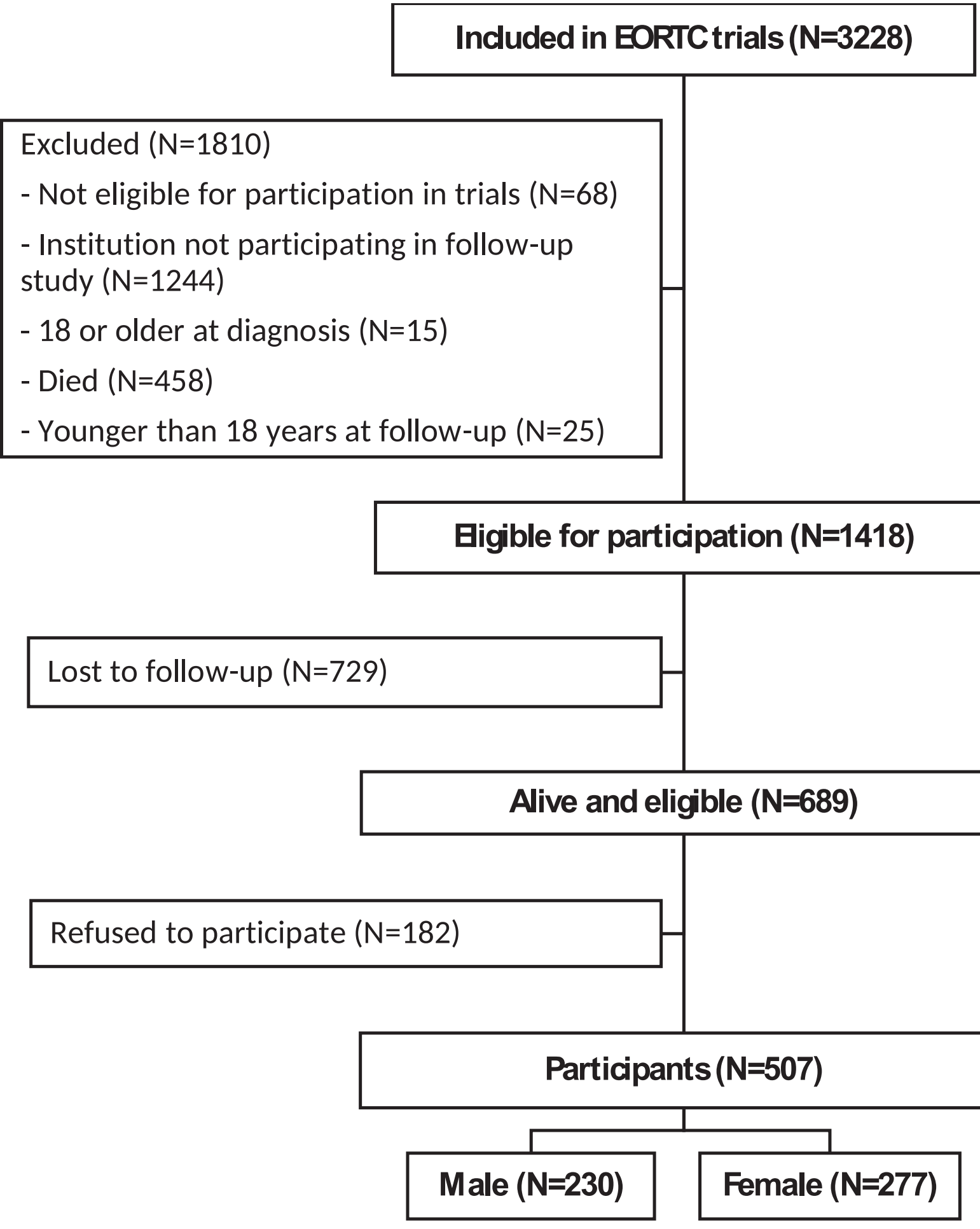

Included in EORTC trials (N=3228)
Excluded (N=1810)
- Not eligible for participation in trials (N=68)
- Institution not participating in follow-up study (N=1244)
- 18 or older at diagnosis (N=15)
- Died (N=458)
- Younger than 18 years at follow-up (N=25)
Eligible for participation (N=1418)
Lost to follow-up (N=729)
Alive and eligible (N=689)
Refused to participate (N=182)
Participants (N=507)
Male (N=230)
Female (N=277)

Table S I. Patient characteristics by responding status.

		Patient lost to follow-up (N=729)	Patient refused to participate (N=182)	Respondent (N=507)	Total (N=1418)
		N (%)	N (%)	N (%)	N (%)
EORTC study					
	N obs	729 (100.0)	182 (100.0)	507 (100.0)	1418 (100.0)
58741		20 (2.7)	12 (6.6)	25 (4.9)	57 (4.0)
58831/2		199 (27.3)	44 (24.2)	109 (21.5)	352 (24.8)
58881		510 (70.0)	126 (69.2)	373 (73.6)	1009 (71.2)
Sex					
	N obs	726 (99.6)	182 (100.0)	507 (100.0)	1415 (99.8)
Male		437 (60.2)	103 (56.6)	230 (45.4)	770 (54.4)
Female		289 (39.8)	79 (43.4)	277 (54.6)	645 (45.6)
Age at diagnosis, years					
	N obs	726 (99.6)	182 (100.0)	507 (100.0)	1415 (99.8)
<6		434 (59.8)	130 (71.4)	332 (65.5)	896 (63.3)
6-9		159 (21.9)	30 (16.5)	105 (20.7)	294 (20.8)
10-17		133 (18.3)	22 (12.1)	70 (13.8)	225 (15.9)
Country					
	N obs	729 (100.0)	182 (100.0)	507 (100.0)	1418 (100.0)
Belgium		259 (35.5)	106 (58.2)	236 (46.5)	601 (42.4)
France		470 (64.5)	76 (41.8)	271 (53.5)	817 (57.6)
Disease					
	N obs	723 (99.2)	182 (100.0)	506 (99.8)	1411 (99.5)
ALL		645 (89.2)	182 (100.0)	498 (98.4)	1325 (93.9)
LBL		78 (10.8)	0 (0.0)	8 (1.6)	86 (6.1)
WBC at diagnosis, x 10□/l					
	N obs	724 (99.3)	181 (99.5)	507 (100.0)	1412 (99.6)
<25		528 (72.9)	125 (69.1)	362 (71.4)	1015 (71.9)
25 - <50		78 (10.8)	27 (14.9)	59 (11.6)	164 (11.6)
≥50		118 (16.3)	29 (16.0)	86 (17.0)	233 (16.5)
CNS involvement at diagnosis					
	N obs	708 (97.1)	179 (98.4)	505 (99.6)	1392 (98.2)
Negative		666 (94.1)	164 (91.6)	479 (94.9)	1309 (94.0)
Questionable or positive		42 (5.9)	15 (8.4)	26 (5.1)	83 (6.0)
Relapse within 1 year from diagnosis					
	N obs	729 (100.0)	182 (100.0)	507 (100.0)	1418 (100.0)
No		722 (99.0)	180 (98.9)	502 (99.0)	1404 (99.0)
Yes		7 (1.0)	2 (1.1)	5 (1.0)	14 1.0)

Abbreviations: ALL: acute lymphoblastic leukaemia, CNS: Central Nervous System, HSCT: haematopoietic stem cell transplantation, NCI: National Cancer Institute, LBL: Lymphoblastic Lymphoma, WBC: White Blood Cells.

Table S II. Characteristics of controls compared to survivors.

	Population control (N=491)	Cancer survivor (N=491)
	N (%)	N (%)
Sex		
Male	216 (44.0)	216 (44.0)
Female	275 (56.0)	275 (56.0)
Age (years)		
18-19	53 (10.8)	53 (10.8)
20-21	78 (15.9)	78 (15.9)
22-23	72 (14.7)	72 (14.7)
24-25	55 (11.2)	55 (11.2)
26-27	59 (12.0)	59 (12.0)
28-29	59 (12.0)	59 (12.0)
30-31	39 (7.9)	39 (7.9)
32-33	20 (4.1)	20 (4.1)
34-35	15 (3.1)	15 (3.1)
36-37	8 (1.6)	8 (1.6)
38-39	13 (2.6)	13 (2.6)
40-44	11 (2.2)	11 (2.2)
45-52	9 (1.8)	9 (1.8)
Median	25.0	25.4
Level of education		
N obs	483 (98.4)	483 (98.4)
No secondary school diploma	1 (0.2)	19 (3.9)
Secondary school diploma, no university degree	152 (31.5)	212 (43.9)
University degree	330 (68.3)	252 (52.2)
Region		
France, rural	99 (20.2)	99 (20.2)
France, urban	164 (33.4)	164 (33.4)
Belgium, Brussels region	15 (3.1)	15 (3.1)
Belgium, Flanders, rural	3 (0.6)	3 (0.6)
Belgium, Flanders, urban	158 (32.2)	158 (32.2)
Belgium, Wallonia, rural	10 (2.0)	10 (2.0)
Belgium, Wallonia, urban	42 (8.6)	42 (8.6)

Table S III. Menstruation history among female survivors.

Endpoint	N / N with available information	% (95% CI)
Menstrual period ever	268 / 272	98.5 (96.3 - 99.6)
Menstrual cycles before diagnosis	21 / 268	7.8 (4.9 - 11.7)
Discontinuation of menstrual cycles during treatment*	16 / 19	84.2 (60.4 - 96.6)
Coming back of menstrual cycles after treatment^	13 / 15	86.7 (59.5 - 98.3)

*among patients with menstrual cycles before diagnosis

^among patients for whom menstrual cycles stopped during treatment