PERGAMON

European Journal of Cancer 37 (2001) 605–612

European Journal of Cancer

www.ejconline.com

Adult height and age at menarche in childhood cancer survivors

E.M. Noorda [a], R. Somers [b], F.E. van Leeuwen [c], T. Vulsma [d], H. Behrendt [a,*] from the Dutch Late Effects Study Group

[a] *Emma Kinderziekenhuis, Department of Pediatric Oncology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

[b] *Division of Medical Oncology, Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

[c] *Netherlands Cancer Institute/Antoni van Leeuwenhoek Ziekenhuis, Department of Epidemiology, Amsterdam, The Netherlands*

[d] *Emma Kinderziekenhuis, Department of Pediatric Endocrinology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

Received 11 July 2000; received in revised form 26 October 2000; accepted 1 December 2000

Abstract

The aim of this study was to assess the long-term effects of cancer treatments on adult height and age at menarche in survivors of various types of childhood cancer. 285 childhood cancer survivors (161 men and 124 women), at least 18 years old and having been off treatment for at least 5 years, were examined. The effects of cranial (CrRT) and craniospinal irradiation (CrSpRT), other treatments and age at diagnosis on adult height and age at menarche were investigated. Patients who did not receive CrRT or CrSpRT, reached normal adult heights. However, a significant reduction in adult height was observed in men and women treated with CrRT or CrSpRT, especially if the treatment was given at the age of 8 years or younger. In girls, CrRT resulted in a significantly earlier menarche, compared with the Dutch population. Chemotherapy, radiation dose and age at menarche did not affect adult height. The relative risk (RR) of attaining an adult height below the 3rd percentile (20% 49/244) of the study population) was 6 times increased (RR = 6.4; 95% confidence interval (CI) 1.46–28.52) after CrSpRT, 4 times (RR = 4.2; 95% CI 1.81–9.63) after Crth and 5 times (RR = 51; 95% CI 2.23–11.59) when irradiation was administered at the age of 8 years or younger. CrRT and CrSpRT and age at treatment are the main determinants of short stature in male and female childhood cancer survivors.

Keywords: Paediatric oncology; Long-term survivors of childhood cancer; Late effects; Cranial irradiation; Craniospinal irradiation; Adult height; Menarche; Age at treatment

1. Introduction

Over the past three decades, the prognosis of children with cancer has greatly improved. At the same time, an increased incidence of long-term sequelae of cancer treatment has been observed. These late effects are both psychosocial and somatic, including the occurrence of second primary tumours, organ failure, infertility and growth impairment. The most important factors influencing human growth are skeletal growth disturbances and hormone deficiencies, mainly growth hormone deficiency and thyroid hormone deficiency. In addition, early puberty may result in short stature.

Most studies on growth impairment have focused on patients treated for acute lymphoblastic leukaemia (ALL) who received prophylactic cranial irradiation [1–7]. Fewer reports have published about the possible effects on growth of irradiation for non-pituitary-related brain tumors [9]. In addition, relatively little is known about the effect of spinal irradiation alone on growth [10–12]. Another frequently reported problem is early menarche. In girls treated for ALL, cranial irradiation has been reported to contribute to an early menarche [2–5]. However, Mills and colleagues state that cranial irradiation appears to have minimal influence on the onset of puberty [8]. Reduced adult height frequently occurs in people previously treated for acute lymphoblastic leukemia (ALL). *Cranial irradiation* can cause endocrine damage, including growth hormone or thyroid

* Corresponding author. Tel.: +31-20-566-5663; fax: +31-20-6917735.

E-mail addresses: hbehrendt@amc.uva.nl (H. Behrendt), emnoorda@hotmail.com (E.M. Noorda), fvleeuw@nki.nl (F.E. van Leeuwen), t.vulsma@amc.uva.nl (T. Vulsma).

0959-8049/01/$ - see front matter
PII: S0959-8049(00)00438-X

hormone deficiency and, consequently, influences adult height. *Spinal irradiation* influences growth through direct skeletal damage. *Chemotherapy* may damage the gonads and possibly has an important impact on growth [1,21]. It is now commonly accepted that cranial irradiation is the most important cause of impaired growth.

Although impairment of growth and early puberty have been documented in children treated for ALL and brain tumors, less attention has been paid to these problems in survivors of other childhood malignancies [13–15]. Therefore, we studied the effect of different cancer treatments and age at treatment on adult height and age at menarche in survivors of various types of childhood cancer.

2. Patients and methods

The study population consisted of 285 survivors of childhood cancer. They visited the Outpatient Clinic for Late Effects of Childhood Cancer in the Academical Medical Center (AMC), Amsterdam, The Netherlands. All adult survivors of childhood cancer at the Emma Kinderziekenhuis/AMC since 1965, are invited to be screened at this outpatient clinic for various late effects of cancer treatment. Survivors are invited for the first screening when they are at least 18 years of age and have been off treatment for at least 5 years. Our study population consisted of the first consecutive 285 ex-patients who were seen between February 1996, when the outpatient clinic started to operate, and January 1997. Of these persons, 161 (56%) were male and 124 (44%) female. Mean age at investigation was 24 years (range 18–39 years). Their mean age at diagnosis of primary cancer was 8.9 years (0–19 years). The mean interval between the last administered treatment and screening visit to the outpatient clinic was 14.6 years (range 5–31 years). Data on diagnosis and treatment are given in Table 1. The study population was representative for the general population of survivors of childhood cancer in our centre with respect to gender and age at

Table 1
Diagnosis and treatment in the study population

Diagnosis		*n* (%)	Cranial irradiation *n* (%)	Craniospinal irradiation *n* (%)	No cranial or craniospinal irradiation *n* (%)
Leukaemia	♂	32 (20)	20 (51)	0	12 (12)
	♀	33 (27)	22 (59)	1 (11)	10 (13)
NHL	♂	25 (16)	9 (23)	0	16 (16)
	♀	14 (11)	9 (24)	0	5 (6)
M. Hodgkin	♂	26 (16)	0	0	26 (25)
	♀	10 (8)	1 (3)	0	9 (12)
Non-pituitary-related brain tumours	♂	27 (17)	5 (13)	20 (100)	2 (2)
	♀	10 (8)	2 (5)	8 (89)	0
Osteosarcoma	♂	18 (11)	0	0	18 (18)
	♀	14 (11)	1 (3)	0	13 (17)
Wilms' tumours	♂	12 (7)	0	0	12 (12)
	♀	15 (12)	0	0	15 (19)
Rhabdomyosarcoma	♂	11 (7)	3 (8)	0	8 (8)
	♀	11 (9)	0	0	11 (14)
Neuroblastoma	♂	3 (2)	0	0	3 (3)
	♀	4 (3)	0	0	4 (5)
Nasopharyngeal tumours	♂	2 (1)	2 (5)	0	0
	♀	2 (2)	2 (5)	0	0
Thyroid tumours	♂	2 (1)	0	0	2 (2)
	♀	1 (1)	0	0	1 (1)
Skin tumours	♂	1 (1)	0	0	1 (1)
	♀	1 (1)	0	0	1 (1)
Testicular tumours		2 (1)	0	0	2 (2)
Ovarian tumours		8 (6)	0	0	8 (10)
Liver tumours	♀	1 (1)	0	0	1 (1)
Total	♂	161 (100)	39 (24)	20 (12)	102 (63)
	♀	124 (100)	37 (30)	9 (7)	78 (63)

NHL, non-Hodgkin's lymphoma.

diagnosis. However, in the study population there was an overrepresentation of children treated for non-pituitary brain tumours, due to a study on the late effects of treatment for brain tumours that was ongoing when the outpatient clinic started. For this study, brain tumour patients were preferentially invited to be screened, resulting in a relatively large group of patients treated with cranial irradiation (CrRT) and craniospinal irradiation (CrSpRT) which served the purpose of this study. Children treated for ALL and non-Hodgkin's lymphoma (NHL) received 18–30 Gy of cranial irradiation. Children with non-pituitary-related brain tumours received 35 Gy to the whole cranium and the spine, with a boost up to 55 Gy on the tumour area.

During the former patients' visit to the outpatient clinic, a detailed history was taken and a complete physical examination was performed by an internist. In all persons, routine laboratory investigations were performed. Specific investigations, related to the expected toxicity of the cancer treatment, were carried out in selected subjects.

We chose to examine adult height as our main outcome measure. We could not study growth patterns throughout the years from treatment until adult height since this study is retrospective and sitting height and body weight were not routinely measured during the study period.

The data used for the present analysis were obtained and analysed as follows: standing height was measured with a calibrated metre. Height was compared with data from the general population in The Netherlands, collected by the Dutch Central Office of Statistics (CBS) [17]. Age at menarche was obtained through information from the patient's chart and, if not reported, through questioning the women and their mothers. In the analysis of determinants of menarcheal age, girls were only included if they fulfilled two criteria: first, they were 10 years or younger at the diagnosis of cancer, because women with a later age at diagnosis have a skewed distribution of this variable to the right, i.e. a later age at menarche, and, secondly, they had an age at menarche at least 1 year after the start of therapy. Mean age at menarche was compared with the standard in The Netherlands [18].

The most important factors determining adult height were defined by means of a multivariate regression analysis. The following independent variables were examined. *Treatment*: CrSpRT (35 and 55 Gy dosage to the tumour area), CrRT (18–30 Gy), chemotherapy and other treatments not including CrRT or CrSpRT. No patients received Total Body Irradiation. Patients who received chemotherapy in addition to CrRT or CrSpRT were classified in the CrRT or CrSpRT groups in the univariate analysis; in multivariate analysis, additional chemotherapy was entered into the model as an independent variable. *Dose of irradiation*: in earlier studies the effect of radiation dose on adult height was studied [19,20]. In our study population it was not possible to perform a clinically relevant analysis on adult height comparing the group receiving 24 Gy to the cranium compared with those who received 18 Gy, because the latter group was too small in this population. Since it is expected that high-dose CrRT impacts final height more than lower-dose cranial irradiation, we did compare two groups receiving more and less than or equal to 30 Gy to the cranium. *Age at diagnosis*: we divided the subjects into two groups with a cut-off point of 8 years at diagnosis. This cut-off point was chosen for two reasons. First, approximately half of the increase in height, reached from birth until adulthood, is attained around this age. Secondly, linear regression analysis showed that a cut-off point chosen at the age of 8 years had the strongest influence on the outcome measures.

Endocrine characteristics: in this study, all subjects had been treated if hypothyroidism had been detected. All subjects included were euthyroid. In the investigated population, 5% became growth hormone-deficient during the time between treatment and screening. All were treated with growth hormone supplementation.

To determine the most important factors in determining an unusual short adult height, below the 3rd percentile (females 157 cm and males 169 cm) [18], we used a multivariate logistic regression analysis. For univariate analysis, we used the Student's *t*-test for independent samples and the one sample *t*-test.

3. Results

3.1. Adult height in male survivors

From 161 male survivors, height was not measured in six. Twenty-one men were between 18 and 20 years old at the time of the investigation and their height could not be compared with the data from the CBS which starts at the age of 20 years. One man was excluded from analysis because he received CrSpRT without dosage to the cranium and could not be included in one of the treatment groups. Thus, the data of 133 men were evaluated.

3.1.1. Univariate analysis

Table 2a shows the results of the univariate analysis of adult height in men. The male population was divided into two age categories, 20–29 and 30–39 years, to take into account the secular trend, which shows that in Western countries an increase in height of the population of 1.5 cm is observed every decade. Mean height of the males in both categories was significantly lower than mean height of their peers in the Dutch population ($P < 0.001$ and < 0.05, respectively).

Table 2
The effect of treatment and age at diagnosis on adult height in childhood cancer survivors

Age and treatment	*n* (%)	Adult height (cm)			
		Mean in study population (S.D.)	*P* value	Range	Mean in Dutch population (S.D.)
(a) Male					
Total	133 (100)				
20–29 years	108 (81)	177.5 (9.4)	$<0.001^a$	157.0–201.0	182.6 (6.7)
30–39 yrs	25 (19)	178.0 (7.0)	$<0.05^a$	165.0–190.0	181.1 (6.7)
Craniospinal irradiation	15 (11)	170.7 (7.8)		157.0–184.0	
⩽8 years at diagnosis	4	161.6 (3.4)	0.001^b	157.0–165.0	
>8 years at diagnosis	11	174.0 (6.0)		165.0–184.0	
Cranial irradiation	33 (25)	172.9 (8.6)		157.0–195.0	
⩽8 years at diagnosis	20	169.4 (6.8)	$<0.005^b$	157.0–179.0	
>8 years at diagnosis	13	178.4 (8.4)		163.0–195.0	
Other treatments	85 (64)	180.7 (7.8)		165.0–201.0	
⩽8 years at diagnosis	28	178.5 (7.7)	$>0.05^b$	165.0–195.5	
⩽8 years at diagnosis	57	181.7 (7.8)		165.0–201.0	
(b) Female					
Total	111 (100)				
20–29 years	94 (85)	164.8 (8.1)	$<0.001^a$	146.0–183.0	169.5 (6.2)
30–39 years	17 (15)	164.6 (6.7)	$<0.05^a$	150.5–178.0	168.1 (6.2)
Craniospinal irradiation	9 (8)	159.0 (7.0)		150.5–168.0	
⩽8 years at diagnosis	2	153.0 (1.4)	$<0.05^b$	152.0–154.0	
>8 years at diagnosis	7	160.7 (7.1)		150.5–168.0	
Cranial irradiation	35 (32)	160.6 (7.0)		146.0–176.0	
⩽8 years at diagnosis	21	158.0 (6.6)	$<0.005^b$	146.0–169.0	
>8 years at diagnosis	14	164.5 (5.8)		157.0–176.0	
Other treatments	67 (60)	167.7 (7.0)		153.0–183.0	
⩽8 years at diagnosis	23	165.5 (6.5)	$<0.05^b$	155.0–178.0	
>8 years at diagnosis	44	168.9 (7.1)		153.0–183.0	

S.D., standard deviation.
[a] *P* value for the difference with the mean adult height in the Dutch population.
[b] *P* value for the difference between groups ⩽8 years at diagnosis and >8 years at diagnosis.

3.1.1.1. Craniospinal irradiation (CrSpRT). Compared with the data from the Dutch population, men in this group attained significantly reduced adult height ($P<0.001$), which was even more pronounced when radiotherapy was administered at the age of 8 years or younger ($P<0.001$). The mean heights in the various study groups were compared with the mean adult height of the group in the Dutch population aged 30–39 years. Boys treated after the age of 8 years also reached a significantly reduced adult height ($P<0.05$), although this reduction was less than in those treated at the age of 8 years or younger.

3.1.1.2. Cranial irradiation (CrRT). Survivors in this group reached significantly smaller adult height as well, compared with the data from the Dutch population ($P<0.001$). The reduction in adult height was strongest in those treated at the age of 8 years or younger ($P<0.001$). However, boys treated with CrRT after the age of 8 years also attained a reduced adult height, not significantly different from the mean height in the Dutch population.

In both group I (CrSpRT) as in group II (CrRT) these differences did not only occur in comparison with the mean adult height in the Dutch population, but also in comparison with the group of patients who received cancer treatments other than CrRT or CrSpRT ($P<0.001$ for both groups). Furthermore, significantly more height loss occurred in patients treated at the age of 8 years or younger in patients who received CrSpRT than in those who received CrRT ($P<0.05$).

Those who had received a cranial irradiation dose higher than 30 Gy had a mean height of 171.9 cm which was not significantly different from the mean adult height of those who received a cranial irradiation dose lower that 30 Gy (mean 172.8 cm).

3.1.1.3. Other cancer treatment. There was no significant height loss in males who had received cancer treatments other than CrRT or CrSpRT.

3.2. Adult height in female survivors

In four out of the 124 women, height was not measured. Eight women were between 18 and 20 years old at the time of investigation and therefore their height could not be compared with the data from the CBS.

One woman was excluded from analysis because she had been treated with spinal irradiation alone and thus could not be included in one of the treatment groups for comparison. Therefore, the data of 111 women were evaluated.

3.2.1. Univariate analysis

Table 2b shows the results of the univariate analysis with regard to adult height in women. The female population was also divided into two age categories, as mentioned above. Mean height of the females in both age categories was significantly lower than the mean height of their peers in the Dutch population ($P < 0.001$ and < 0.05, respectively).

3.2.1.1. Craniospinal irradiation (CrSpRT). As in men, women in this group attained significantly reduced adult height compared with women in the Dutch population ($P < 0.05$). Adult height was even more reduced when women were treated at the age of 8 years or younger ($P < 0.05$). However, this group was too small to draw firm conclusions. Those women who were irradiated after the age of 8 years also reached a significantly reduced adult height ($P < 0.05$).

3.2.1.2. Cranial irradiation (CrRT). The women treated with CrRT also attained reduced adult height which was significantly different from the Dutch population ($P < 0.001$). As in men, the reduction was most pronounced if they were treated at the age of 8 years or younger ($P < 0.001$). Women who had been treated with CrRT after the age of 8 years also attained significantly smaller adult height ($P < 0.05$).

As in men, the reduction in adult height after CrRT or CrSpRT was not only significant in comparison with the Dutch population, but also when compared with survivors who received other cancer treatments (P values of 0.001 and < 0.001 for groups I and group II, respectively).

Those women who received a cranial irradiation dose higher than 30 Gy attained a mean adult height of 158.9 cm, which was not significantly different from the mean adult height of those who received a dose below 30 Gy to the cranium (mean 160.8 cm).

3.2.1.3. Other cancer treatments. There was no significant height loss in females who had received other cancer treatments than CrRT or CrSpRT.

3.2.2. Multivariate linear regression analysis

CrSpRT showed the strongest correlation with adult height ($B = 10.047$ and $B = 9.165$ in males and females, respectively, $P < 0.001$). Diagnosis at the age of 8 years or younger was also significantly associated with adult height (males: $B = 6.255$, $P < 0.001$; females: $B = 4.654$, $P = 0.001$). CrRT was also strongly associated with short stature (males: $B = 5.715$, $P = 0.001$; females $B = 5.821$, $P < 0.001$). In this analysis, the influence of chemotherapy, administered in addition to CrRT or CrSpRT, was also examined. The influence of the dose of irradiation was analysed as well. Neither chemotherapy nor irradiation dose were important factors in determining adult height in men and women. In women, the influence of the age at menarche on adult height was also examined, but this was not a significant determinant.

3.2.3. Multiple logistic regression analysis

To define which variables are of major importance in determining whether boys and girls attain adult height below the 3rd percentile (females below 157 cm and males below 169 cm), a multiple logistic regression analysis was conducted. A group of 49 survivors had attained adult height below the 3rd percentile. The results are shown in Table 3. As in the linear regression analysis, CrRT or CrSpRT and age at diagnosis at the age of 8 years or younger, were most important factors in reducing adult height. Gender, additional chemotherapy and radiation dose did not significantly increase the risk of attaining an unusual short stature.

3.3. Age at menarche

From 124 women, age at menarche could not be obtained accurately in 27. Nineteen women reached their menarche before therapy commenced, 18 women were older than 10 years at diagnosis and three women received hormonal treatment to induce their menarche. Therefore, 57 women were available for analysis. Because of this small number, only a limited analysis was possible.

Table 3
Results of multiple logistic regression analysis: determinants of adult height below 3rd percentile[a]

	Relative risk (Exp (B))	P value	95% Confidence interval	
			Lower	Upper
Craniospinal irradiation versus no craniospinal irradiation	6.4	< 0.05	1.46	28.52
Cranial irradiation versus no cranial irradiation	4.2	< 0.005	1.81	9.63
Age at diagnosis $\leqslant$ 8 years versus age at diagnosis $>$ 8 years	5.1	< 0.005	2.23	11.59

[a] Females below 157 cm and males below 169 cm.

The mean age at menarche in the study population was approximately the same as the Dutch standard (13.0 years versus 13.2 years). However, when comparing different treatment groups as with adult height, there seemed to be some important effects on the age at menarche.

3.3.1. Univariate analysis

Compared with age at menarche in the Dutch population, age at menarche in girls who received CrRT was significantly earlier (mean 12.4 years, $P=0.001$). In addition, in comparison with girls who received other cancer treatments ($n=30$), girls who received CrRT ($n=25$) showed a significantly earlier menarche ($P=0.005$). Girls who received no CrRT or CrSpRT, reached menarche at a normal age (mean age of 13.3 years). In contrast, the two girls who had been treated with CrSpRT had a later mean age at menarche (mean age of 15.3 years) than the mean in the Dutch female population. However, because of the very small number of females thus treated ($n=2$), these findings are not conclusive. Unfortunately, when the effect of age at diagnosis on age at menarche was studied, the groups proved to be too small to perform a meaningful analysis.

4. Discussion

We found that male and female childhood cancer survivors attained reduced adult heights, compared with published data on height in the general population. Our data confirm those of other studies showing that CrRT is a major contributing factor for this observation [1–4,6,13].

CrRT influences growth through damage to the hypothalamo-pituitary axis, which can result in growth hormone or thyroid hormone deficiencies. The group with CrSpRT reached the smallest adult height. This confirms earlier findings in children treated for ALL in a study described by Schriock and colleagues [7]. In contrast, Robison and colleagues found no significant difference in adult height between children treated for ALL with CrSpRT only, compared with those treated with CrRT only [16]. From our study, it appears that spinal irradiation has an additional impact on adult height. An average loss in height from spinal irradiation of 5–7 cm has previously been reported [10]. The greater reduction in adult height in those who underwent CrSpRT compared with those who received CrRT could be due to two mechanisms. First, growth impairment occurs not only due to hormone deficiencies, but also through direct skeletal damage. Secondly, we assumed that those who received higher doses of cranial irradiation would attain a smaller adult height. The children who received CrSpRT (non-pituitary-related brain tumours), did receive higher irradiation doses ($\geqslant 30$ Gy) compared with those who received only CrRT (ALL and lymphomas, <30 Gy). Nevertheless, in our analysis a higher dose of cranial irradiation does not appear to have had a significant impact on growth. Therefore, the smaller adult height resulting after treatment with CrSpRT should be mainly contributed to the additional direct skeletal damage caused by the spinal irradiation.

We also examined the effect of chemotherapy, administered in combination with CrRT or CrSpRT. Additional chemotherapy did not have any significant influence on adult height. In addition, adult height in childhood cancer survivors who had received other cancer treatments than CrRT or CrSpRT was not significantly reduced compared with the mean height in the Dutch population. As Hokken-Koelega and colleagues describe in a study on children treated for ALL, it could be that a temporary height loss occurs after chemotherapy and that a subsequent catch up is seen during puberty so that they attain normal adult height [21]. Since we only looked at the final height measurements, we cannot confirm this finding.

In our study, we found no clear association between age at menarche and growth in women. This is in contrast with the general assumption that an early menarche increases the risk of attaining short stature. In our study population, no women attained their menarche at an unusually early age and, therefore, we could not assess the effect of unusual early menarche on growth.

Our study also supports the finding in earlier reports that age at the time of irradiation is an important modifier of the radiation related effect on growth [1,2,9,11]. In both males and females, treatment at the age 8 years or younger caused a greater reduction in adult height than treatment after this age. Both findings can be explained by the following mechanisms: first, it might indicate that the hypothalamo-pituitary axis is more sensitive to irradiation when patients are relatively young [22]. Secondly, it could also simply reflect the fact that children have reached a relatively smaller portion of their adult height at the age of 8 years or younger than after this age. Consequently, the effect of growth retardation on adult height is larger when it occurs at a young age than when patients are older and have already reached a large part of their adult height. Interestingly, males who had CrRT after the age of 8 years attained almost normal adult height. This was not the case for females, who were still significantly smaller if treated with CrRT after the age of 8 years. Possibly, in women a dual endocrinopathy of early puberty and growth hormone insufficiency influences adult height [23]. In our study, this is reflected in the observation that CrRT also seems to result in an earlier menarche, which is known to be an important determinant of short stature [11]. However, as stated earlier, we could not confirm the association between age at menarche and

adult height primarily because of the small numbers in the subgroups. Importantly, the most dramatic decrease in adult height was seen in both men and women who were treated with CrRT or CrSpRT at the age of 8 years or younger. We specifically examined risk factors for an exceptionally short stature, below the 3rd percentile. For females, this was below 157 cm, for males, below 169 cm. Receiving CrSpRT, i.e. a cranial irradiation dose >30 Gy combined with spinal irradiation, strongly increased the risk of being unusually small (relative risk (RR) = 6.4). Children who received CrRT, i.e. cranial irradiation dose $\leqslant 30$ Gy, also had a higher risk of attaining an exceptionally small adult height (RR = 4.2), but their risk was lower than in the first group. Radiation treatment at the age of 8 years or younger was an independent determining factor defining the risk of becoming unusually small (RR = 5.1). Again, a cranial irradiation dose higher than 30 Gy, as an independent factor, did not appear to have significantly more impact on adult height than a cranial irradiation dose lower than or equal to 30 Gy. In addition, chemotherapy and age at menarche had no significant impact on reaching an exceptionally short stature.

One of the possible ways through which cranial irradiation may cause short stature, is growth hormone deficiency (GHD). Only 5% of our study population appeared to be growth hormone (GH) insufficient after treatment and were treated with GH. Their adult height was not significantly different from the rest of the study population; however, this group was very small. In this study, we could not examine GHD further as a possible cause of reduced adult height. From this retrospective study, it is therefore not possible to draw conclusions on the relationship between GHD and short stature. However, it would be interesting to find out if GH levels are important in identifying those patients who are at risk of reaching a short stature. Earlier reports are not conclusive about the causative role of radiation-induced GHD in reduced adult height. For example, Sklar and colleagues state in a study of children treated for ALL that it remains difficult to precisely define the role of GHD in attaining a short adult stature, since individual growth patterns seem to correlate poorly with the results of GH testing in children treated for ALL with CrRT [24,25]. Davies and colleagues report from a study on children treated for ALL that the cause of growth impairment is probably multifactorial with GHD, chemotherapy, early puberty and steroids all having a role [6]. However, Darendeliler and colleagues demonstrated in a study of children treated with radiotherapy for brain tumours that GH is effective in increasing height after GHD due to CrRT or CrSpRT, suggesting that GH is crucial in attaining normal adult height [12]. Leiper and colleagues stated that treatment with GH for GHD causes an increase in growth in ALL survivors, but more complete long-term research needs to be done to support this finding [15]. In our study, any association between adult height and GH administration would be confounded by the indication of its use and therefore this can only be assessed in a randomised clinical trial.

Our study has shown that CrRT and CrSpRT, especially at a young age, have an important influence on growth. Consequently, children treated with radiotherapy to the cranium for childhood cancer have a high risk of attaining a short stature. This reflects the intensity of the cancer treatments received, which may have an impact on psychosocial well-being as a child, teenager and adult. Furthermore, those who have attained reduced adult height from CrRT can be at risk for the development of GHD syndrome, consisting of obesity, reduced muscle mass, lipid abnormalities, fatigue and reduced quality of life [26]. These data confirm our policy, although evidence of its effectiveness from clinical trials is lacking, to treat children with growth hormone as soon as growth retardation, caused by GHD, occurs in order to avoid metabolic and cardiovascular problems. Although CrRT has been abandoned from the treatment schemes for non-high risk childhood ALL, we have no alternatives for children with leukaemic relapses in the central nervous system and children with tumours in the skull. More research is necessary in order to find other effective cancer therapies for these patients.

Acknowledgements

W.J. Klokman, MD MSc, for support with the statistical analysis.

References

1. Mohnike K, Dörffel W, Timme J, *et al*. Final height and puberty in 40 patients after antileukemic treatment during childhood. *Eur J Pediatr* 1997, **156**, 272–276.
2. Cicognani A, Cacciari E, Rosito P, *et al*. Longitudinal growth and final height in long-term survivors of childhood leukaemia. *Eur J Pediatr* 1994, **153**, 726–730.
3. Moëll C, Marky I, Hovi L, *et al*. Cerebral irradiation causes blunted pubertal growth in girls treated for acute leukemia. *Med Pediatr Oncol* 1994, **22**, 375–379.
4. Didcock E, Davies HA, Didi M, *et al*. Pubertal growth in young adult survivors of childhood leukemia. *J Clin Oncol* 1995, **13**, 2503–2507.
5. Quigley C, Cowell C, Jimenez M, *et al*. Normal or early development of puberty despite gonadal damage in children treated for acute lymphoblastic leukemia. *N Engl J Med* 1989, **21**, 143–151.
6. Davies HA, Didcock E, Didi M, Ogily-Stuart A, Wales JKH, Shalet SM. Growth, puberty and obesity after treatment for leukemia. *Acta Paediatr Scand* 1995, **411**(Suppl.), 45–50.
7. Schriock EA, Schell MJ, Carter M, Hustu O, Ochs JJ. Abnormal growth patterns and adult short stature in 115 long-term survivors of childhood leukemia. *J Clin Oncol* 1991, **9**, 400–405.
8. Mills JL, Fears TR, Robison LL, Nicholson HS, Sklar CA, Byrne J. Menarche in a cohort of 188 long term survivors of acute lymphoblastic leukemia. *J Pediatr* 1997, **131**, 598–602.

9. Clarson CL, Del Maestro RF. Growth failure after treatment of pediatric brain tumors (www. pediatrics.org; **103**, 1999, e37).
10. Ogilvy-Stuart AL, Shalet SM. Growth and puberty after growth hormone treatment after irradiation of brain tumors. *Arch Dis Child* 1995, **73**, 141–146.
11. Shalet SM, Gibson B, Swindell R, Pearson D. Effect of spinal irradiation on growth. *Arch Dis Child* 1987, **2**, 461–464.
12. Darendeliler F, Livesey EA, Hindmarsh PC, Brook CGD. Growth and growth hormone secretion in children following treatment of brain tumours with radiotherapy. *Acta Paediatr Scand* 1990, **79**, 950–956.
13. Talvensaari KK, Knip M, Lanning P, Lanning M. Clinical characteristics and factors affecting growth in long-term survivors of cancer. *Med Pediatr Oncol* 1996, **26**, 166–172.
14. Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. *J Clin Endocrin Metab* 1994, **78**, 1282–1286.
15. Leiper AD, Stanhope R, Preece MA, Grant DB, Chessells JM. Precocious or early puberty and growth failure in girls treated for acute lymphoblastic leukaemia. *Horm Res* 1988, **30**, 72–76.
16. Robison L, Nesbit ME, Sather HN, Meadows AT, Ortega JA, Hammond GD. Height of children succesfully treated for acute lymphoblastic leukemia: a report from the late effects study committe of children's cancer study group. *Med Pediatr Oncol* 1985, **13**, 14–21.
17. Centraal Bureau voor de Statistiek. *Vademecum Gezondheidsstatistiek*, 1996.
18. Roede MJ, van Wieringen JC. Groeidiagrammen 1980. *TSG* 1985, **63**, 1–34.
19. Lannering B, Rosberg S, Marky I, Moëll C, Albertsson-Wikland K. Reduced growth hormone secretion with maintained periodicity following cranial irradiation in children with acute lymphoblastic leukaemia. *Clin Endocrin* 1995, **42**, 153–159.
20. Schmiegelow M, Lassen S, Weber L, Poulsen HS, Hertz H, Muller J. Dosimetry and growth hormone deficiency following cranial irradiation of childhood brain tumors. *Med Pediatr Oncol* 1999, **33**, 564–571.
21. Hokken-Koelega ACS, Van Doorn JWD, Hählen K, Stijnen T, De Muinck K-S, Drop SLS. Long-term effects of treatment for acute lymphoblastic leukemia with and without cranial irradiation on growth and puberty: a comparative study. *Pediatr Res* 1993, **33**, 577–582.
22. Brauner R, Czernichow P, Rappaport R. Greater susceptibility to hypothalamo-pituitary irradiation in younger children with acute lymphoblastic leukemia. *J Pediatr* 1986, **108**, 332.
23. Uruena M, Stanhope R, Chessels JM, Leiper AD. Impaired pubertal growth in acute lymphoblastic leukaemia. *Arch Dis Child* 1991, **66**, 1403–1407.
24. Sklar C, Mertens A, Walter A, Mitchell D, *et al.* Final height after treament for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrays of cranial irradiation. *J Pediatr* 1993, **123**, 59–64.
25. Shalet SM, Price DA, Beardwell CG, Morris Jones PH, Pearson D. Normal growth despite abnormalities of growth hormone secretion in children treated for acute leukemia. *J Pediatr* 1979, **94**, 719–722.
26. Cuneo RC, Salomon F, McGauley GA, Sönksen PH. The growth hormone deficiency syndrome in adults. *Clin Endocrinol* 1992, **37**, 387–397.