Medical and Pediatric Oncology 21:117–121 (1993)

# Prophylactic Cranial Irradiation Increases the Risk of Testicular Damage in Adult Males Surviving ALL in Childhood

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By combining three series of Scandinavian patients, we were able to compare the late testicular sequelae in 41 adult males whose therapy had included chemotherapy alone or chemotherapy with cranial irradiation without other radiotherapy for ALL in childhood. In multivariate analysis, cranial irradiation was associated with a decrease of 5.7 (95% confidence limits 1.5–9.9) cm ($P = 0.010$) in height, and a decrease of 4.8 (0.3–9.2) ml ($P = 0.036$) in testicle size. Cyclophosphamide was associated with increases of 8.2 (−0.5–16.9) ($P = 0.065$) and 3.9 (0.3–7.4) U/L ($P = 0.036$) in serum FSH and LH concentrations, respectively. Of the 12 patients who had received both cranial irradiation and cyclophosphamide therapy, 4 (33%) had delayed pubertal development as compared with 1 (3.5%) of the other 29 patients ($P = 0.008$). Patients 12–16 years of age at diagnosis had larger testicles ($P = 0.051$) and higher testosterone concentrations ($P = 0.026$) than others. Neither sexual activity nor semen findings correlated with the preceding treatment. Our data indicate that prophylactic cranial irradiation may be associated with impaired growth and pubertal development in boys with ALL.


**Key words:** boys, testicle size, serum FSH and LH, sexual drive, sperm quality

## INTRODUCTION

Chemotherapy in childhood may lead to testicular damage of variable degree, including endocrine dysfunction and failure of sperm production. Testicular irradiation is followed by impairment of function to a dose dependent degree [1–3]. No other risk factors have been identified in detail, although certain chemotherapeutic agents, including cyclophosphamide, cytosine arabinosine, and cisplatin [4–7], appear to be particularly harmful. The extent to which testicular dysfunction is a direct result of cranial irradiation in childhood has been difficult to distinguish from the part played by chemotherapy and other factors, because in the 1970s patients with acute lymphoblastic leukemia (ALL), who are now of adult age, virtually all received cranial irradiation.

We were able to study a Nordic population of 41 males over 18 years of age who had survived ALL and compare the late sequelae of chemotherapy alone with those of chemotherapy and cranial irradiation without other radiotherapy. This approach was possible because prophylactic cranial irradiation has not been used systematically in Norway, whereas it has been in common use in Denmark and Finland.



## PATIENTS AND METHODS

Our series comprised 41 males who had survived ALL in childhood in Copenhagen (n = 13), Helsinki (n = 16), and Oslo or Bergen (n = 12), who were aged 18–27 years, who had received chemotherapy only or cranial irradiation of 20–24 Gy without other radiotherapy, and whose chemotherapy had been discontinued more than a year earlier. The study protocol was approved by the Ethics committees of the four hospitals. The median age of the patients at initial diagnosis had been 7.5 years, with a range from 1 to 16 years. The mean age (± SEM) was 8.5 ± 0.6 years. The average time between diagnosis and this study was 15.2 years, the range being from 4 to 25 years. Of the 41 patients, 33 were between 18 and

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Received January 11, 1991; accepted November 18, 1991.

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22 years, 2 were between 22 and 24 years, and 6 were between 24 and 27 years at the time of this study.

All 41 patients had received intravenous vincristine, and oral prednisone, 6-mercaptopurine, and methotrexate. In addition, asparaginase (n = 33), cyclophosphamide (n = 23), adriamycin (n = 21), and cytosine arabinosine (n = 9) had been used. In 32 patients intravenous infusions of high-dose methotrexate were used in combination with intrathecal methotrexate [8]. Most of the patients had been treated for 3 years [9].

Of the 41 patients, 24 had received chemotherapy only (9 from Denmark, 4 from Finland, and 11 from Norway) and 17 had received cranial irradiation of 20–24 Gy without other radiotherapy (4 from Denmark, 12 from Finland, and 1 from Norway).

Three patients had been started on testosterone supplementation from 4 to 9 years earlier. Their mean concentration of testosterone was lower (9.8 U/L, at 2 weeks after the preceding injection of testosterone) than that of the rest of the patients at the time of the study. All 3 patients had hypergonadotropic hypogonadism and had received cranial radiotherapy. Of the 41 patients, none had received growth hormone and/or thyroid hormone.

Length in cm, weight in kg, and sitting height in cm were measured. Sitting height was calculated in percent of length. Body mass index (BMI) was estimated from weight and length (kg/length in $m^2$).

Pubertal stage was determined according to Tanner. Testicle lengths and widths in mm were measured manually. Testicle size was estimated in ml from 0.52 × length (cm) × width ($cm^2$), according to Hansen and With [10]. The mean value for the two testicles was used. Our reference values were size measurements from 34 healthy Finnish medical students aged 22–25 years: median 26 ml, range 20–40 ml.

A serum sample was taken from each patient in the morning for FSH, LH, and testosterone assays. Serum FSH and LH concentrations were measured with ultrasensitive time-resolved immunofluoro-metric assays [11]. Serum testosterone was measured by RIA.

Sexual activity was estimated from detailed discussions with the 41 patients, 39 of whom gave this information. During the discussion, the frequencies of masturbation and sexual intercourse were recorded and scaled as follows: never, only once, only a few times, once a month, once a week, and twice a week or more frequently.

We aimed to have a semen sample for analysis from every patient. However, this was obtained from only 18 patients. The semen sample was collected by masturbation, either in the clinic or at home immediately before the appointment, after an abstinence period of at least 3 days. The parameters determined included ejaculate volume, sperm density, sperm count/ml, percentage of mobile sperm, grade of motility, life-span, agglutination, percentages of sperms with morphologically abnormal heads, midpieces, or tails, and total percentage of abnormal sperm [12]. Normospermia was defined as: 1) ejaculate volume >= 2.0 ml; 2) sperm concentration >= 20 million/ml; 3) sperm motility >= 50%; 4) life-span >= 48 h; and 5) structural anomalies in < 50% of sperm cells. All five requirements had to be fulfilled. Oligospermia was defined as a sperm concentration of < 20 million/ml.

## STATISTICAL METHODS

The Mann-Whitney U test, the Kruskal-Wallis test, and the chi square test were used to compare different groups. A forward-stepping multiple linear regression analysis was used to identify factors independently associated with body size (height, weight, sitting height, and BMI), testicle size, and serum hormone concentrations (FSH, LH, testosterone). A forward-stepping logistic regression analysis was used to identify the factors independently associated with delayed pubertal development and sexual activity. The 95% confidence limits were calculated as the coefficient ± 1.96 S.E. Because of the very limited number of observations, no attempts were made to use multivariate methods in analyzing associations among the results of semen analysis and preceding therapy. Since age at diagnosis was not linearly associated with the risk of having abnormal clinical or laboratory findings, for the purposes of multivariate analyses the patients were divided into three groups according to age at diagnosis: 1–5.9 years old (n = 16), 6–11.9 years old (n = 13), and 12–16 years old (n = 12).

## RESULTS

In general, the height, weight, sitting height, and BMI of the patients were within normal limits (Table I). However, patients who had received prophylactic cranial irradiation were shorter than the others (Table II). In multivariate analysis, cranial irradiation was the only risk factor associated with shorter stature; it decreased height by 5.7 cm (95% confidence limits 1.5–9.9 cm) ($P = 0.010$). Cytostatic agents were not associated with subsequent body size. No risk factors were associated with weight or sitting height, but patients 12 years or more of age at diagnosis tended to have slightly lower BMIs (20.3) than the other patients (22.6; 95% confidence limits for the difference 0.1–4.4, $P = 0.039$). BMI was > 24.0 in 5 patients and < 20.0 in 14 patients. No association was observed between BMI and any of our criteria of testicular or sexual function.

Pubertal development was generally within normal limits, although 5 patients—all less than 20 years old at

**TABLE I. The Association Among Age at Diagnosis, Therapy, Clinical Characteristics, and Serum Hormone Levels in 41 Adult Males Surviving ALL in Childhood***

| | All patients (n = 41) | Age at diagnosis (years) 1-5 (n = 16) | 6-11 (n = 13) | 12-16 (n = 12) | P |
|---|---|---|---|---|---|
| Height, cm | 177.1 (7.1) | 175.0 (4.5) | 179.5 (6.4) | 177.3 (9.8) | 0.166 |
| Weight, kg | 68.9 (12.3) | 69.5 (14.5) | 72.6 (12.3) | 64.0 (7.4) | 0.142 |
| SH, %[a] | 51.1 (2.6) | 51.9 (2.0) | 50.8 (2.3) | 50.4 (3.5) | 0.246 |
| BMI, kg.m[b] | 21.9 (3.2) | 22.7 (4.1) | 22.5 (3.0) | 20.3 (1.1) | 0.082 |
| Testicle, ml | 13.6 (7.5) | 12.7 (5.2) | 11.3 (4.1) | 17.4 (11.4) | 0.382 |
| FSH, U/L[c] | 8.8 (14.1) | 6.8 (6.1) | 12.4 (24.1) | 7.8 (4.8) | 0.449 |
| LH, U/L[c] | 6.9 (5.8) | 5.1 (2.6) | 8.1 (9.3) | 7.6 (3.1) | 0.257 |
| Testosterone, U/L | 19.0 (7.1) | 17.9 (8.6) | 16.9 (5.9) | 22.2 (5.5) | 0.076 |
| Cranial RT, n | 17 | 8 | 5 | 4 | 0.652 |

*All values are means (SD), unless otherwise indicated.
[a]Sitting height.
[b]Body mass index.
[c]Reference values 2-10 U/L.

**TABLE II. The Association Among Prophylactic Cranial Irradiation (20-24 Gy), Cytostatic Therapy and Subsequent Clinical and Laboratory Data in 41 Adult Males Surviving ALL in Childhood***

| | No cranial irradiation (n = 24) | Cranial irradiation (n = 17) | P |
|---|---|---|---|
| Height, cm | 179.4 (6.5) | 173.8 (6.6) | 0.015 |
| Weight, kg | 71.1 (14.2) | 65.8 (8.4) | 0.181 |
| Sitting height, % | 50.5 (3.1) | 52.1 (1.4) | 0.411 |
| BMI, kg/m | 22.0 (3.7) | 21.8 (2.7) | 0.989 |
| Testicle size, ml | 15.8 (8.8) | 10.6 (3.8) | 0.028 |
| FSH, U/L[a] | 6.6 (4.8) | 12.1 (21.1) | 0.832 |
| LH, U/L[a] | 6.0 (3.4) | 8.2 (8.1) | 0.456 |
| Testosterone, U/L[b,c] | 20.2 (6.7) | 17.0 (7.5) | 0.242 |

*Values are means (SD).
[a]Reference value 2-10 U/L.
[b]Reference value 11-40 U/L.
[c]The three patients receiving testosterone supplementation were excluded from this analysis.

the time of the study—had not yet reached Tanner stage P5 G5. Of these 5 patients, 4 had received both cranial irradiation and cyclophosphamide. The associations between delayed puberty and cranial irradiation without cyclophosphamide ($P = 0.062$) or cyclophosphamide therapy without cranial irradiation ($P = 0.250$) were not statistically significant. However, of the 12 patients who had received both cranial irradiation and cyclophosphamide therapy, 4 (33%) had delayed pubertal development as compared with 1 (3.5%) of the other 29 patients ($P = 0.008$). In multivariate analysis no single risk factors for delayed puberty were identified.

Many patients had small testicles; the mean testicular size was 13.6 ml (Table I). Six patients had testicles of 20 ml or larger; all had received chemotherapy only (Fig. 1). In multivariate analysis, two factors were independently associated with testicular size. Cranial irradiation was associated with a decrease in testicular size of 4.8 (0.3–9.2) ml ($P = 0.036$), whereas patients > 12 years old at the time of diagnosis had larger testicles than the others by 4.8 (0–9.6) ml ($P = 0.051$). Various chemotherapeutic agents had no independent effect on testicular size.

The mean serum testosterone concentration in the 38 patients who were not receiving exogenous testoterone at the time of the study was 19 U/L (Table I). The corresponding concentrations in the three patients receiving testosterone were 4.9, 13.0, and 13.0 U/L, respectively. When all patients were included in the multivariate analysis, patients 12 years or more of age at diagnosis had higher serum testosterone levels than the others by 5.5 (0.7–10.4) U/L ($P = 0.026$). When the three patients receiving testosterone were excluded from the analysis, the effect of age at diagnosis was reduced to 4.7

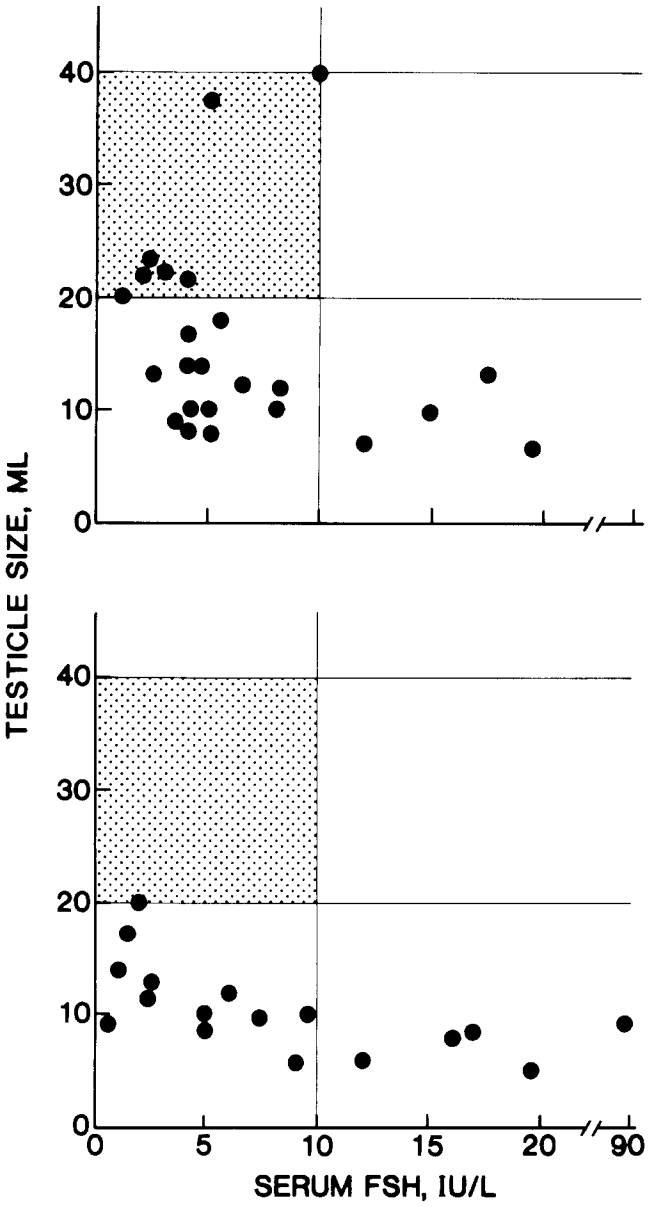


**Fig. 1.** Testicle size (ml) and serum concentration of FSH (IU/L) in patients (age 18–27 years) who had survived ALL in childhood and received either chemotherapy alone (**upper**), or chemotherapy and cranial irradiation (**lower**).

(−0.1–9.6) U/L ($P = 0.057$). Similarly, the effect of cranial irradiation was reduced from −3.9 (−8.4–0.5) U/L ($P = 0.081$) to −3.0 (−7.7–1.8) U/L ($P = 0.211$).

No chemotherapeutic agents were independently associated with serum testosterone levels. In contrast, the only risk factor for abnormal serum FSH and LH levels was cyclophosphamide, which was associated with increases of 8.2 (−0.5–16.9) U/L ($P = 0.065$) and 3.9 (0.3–7.4) U/L ($P = 0.036$) in FSH and LH concentrations, respectively.

Of the 39 patients for whom we had the relevant information, 4 were married or lived with a woman. There was no association between sexual activity and age at the time of the study ($P = 0.411$). Eighteen patients had never experienced sexual intercourse. On the other hand, 13 patients (the 4 married patients included) reported that they generally had sexual intercourse once a week or more frequently. There was no correlation between sexual activity and preceding therapy. The lack of sexual activity was not compensated for by increased frequency of masturbation.

Of the 18 patients from whom a semen sample was obtained, 3 had azoospermia and 7 had oligozoospermia. No significant association was observed between the sperm count and the preceding treatment. No patient fulfilled the criteria of normospermia since of the 8 patients with normal sperm concentrations 8 had asthenozoospermia, 4 had teratozoospermia, and 3 had hypospermia. Among the 18 patients, the average ejaculate volume was 2.8 ± 0.3 ml, with a range from 0.5 to 5.0 ml. No association was observed between the semen volume and the different treatment categories.

## DISCUSSION

We detected some specificity in the types of testicular damage in adult men, with ALL in childhood, who had received chemotherapy, either alone or with cranial radiotherapy. The damage seemed to be worse after cranial irradiation and cyclophosphamide.

Testicle size may give a rough estimate of the degree of damage. Measurement of testicle size is easy to carry out even during puberty [13]. However, the overlap of many values indicates that tolerance of the harmful late effects of these antileukemic therapies is highly variable. Thus, individual advice concerning the putative damage may be difficult to give.

The conclusions drawn of testicle size as a measure of testicular damage may depend on the method by which testicle size is determined and the range of reference values. The available methods include the Prader orchidometer, by which sizes of 25, 20, 15, 12, 10 ml, and so on may be identified [14], the mean testicular index determined by length and width of testicles [13], and the estimation of testicle size in ml from 0.52 × length (cm) × width ($cm^2$), according to Hansen and With [10]. The two last mentioned methods should result in more accurate individual results than those categorized by the Prader orchidometer. In analogous fashion, the reference values may depend on the method of estimation [10,13,14].

In contrast to our conclusions, recent Childrens Cancer Study Group data indicate that cranial radiation therapy of 18 or 24 Gy did not reduce testicular volume in any patient surviving ALL in childhood, although testicular volume was reduced after craniospinal radiation therapy with or without extended abdominal radiation therapy in 50, or 12%, of the cases, respectively [15]. The median age at the time of their last evaluation was 14.5 years, which took place a median of 5.0 years after discontinuing therapy. Of the 17 patients received cranial radiation therapy, 5 were 18 years or more of age. In these 5 patients the testicular volumes were either 20 or 25 ml as estimated by a Prader orchidometer [15]. The small number of adult patients, probably a lower dose of radiation therapy in many of the patients, the use of categorizing method to estimate testicular volume, and the selection of low reference values for comparison (12–22 ml in adults) may explain the differences with our results.

In accordance with earlier findings [7], we observed no significant association between age at diagnosis and the risk of subsequent gonadal damage, except in patients 12 years or more at diagnosis in whom the risk was lower by some criteria.

No major effects on libido or frequency of intercourse have been noted in two studies of adult patients with nonseminomatous germ cell tumors of the testis [16] or Hodgkin's disease [17]. A third study of adult males with Hodgkin's disease indicated a greater decrease in libido as a consequence of the treatment [18]. Among our long-term survivors of ALL in childhood, decreased sexual activity was evident. Half of them had never experienced sexual intercourse, and the fact that a different 50% of them were unwilling or unable to produce a semen sample may be additional evidence for some defect in sexual drive. Earlier experiences [3,19] indicate that a semen sample is obtainable from almost all adolescents who have survived solid tumors in childhood. Thus, in this regard the patients who survived leukemia may have been more affected. This hypothesis fits with recent observations that only one-third of adolescent males who survived childhood leukemia reached normal psychosexual development. Of the corresponding survivors of solid tumors, two thirds developed normally [19]. Our present data suggest that the reason for the difference in psychosexual development is not cranial irradiation.

## ACKNOWLEDGMENTS

We are indebted to the Nordic Society of Pediatric Hematology and Oncology for its cooperation.

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