Original Article

Growth and Endocrine Function in Long-term Adult Survivors of Childhood Stem Cell Transplant

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Abstract. The number of long-term surviving stem cell transplant (SCT) recipients has increased steadily, and attention has now extended to the late complications of this procedure. The objective of this study was to investigate relationship among growth and endocrine functions in long-term adult survivors of childhood SCT. The inclusion criteria of this study were survival at least 5 yr after SCT and achievement of adult height. Fifty-four patients (39 males) fulfilled these criteria and were included in this study. Growth was mainly evaluated by height standard deviation score (SDS) and individual longitudinal growth curves. Among the 54 patients, those that received SCT before 10 yr of age showed significantly greater reductions in changes in height SDS (mean –1.75, range –4.80 to –0.10) compared with those that received SCT at or after 10 yr of age (mean –0.50, range –1.74 to 1.20; P<0.001). The mean loss of height for all patients who received SCT during childhood was estimated to be approximately 1 SDS/6.5 yr (r=0.517). Individual longitudinal growth curves indicated that a significant growth spurt was absent in severe short stature patients during the pubertal period without severe endocrine dysfunctions including GH deficiency. The incidence of growth disorder in long-term adult survivors depends on the age at SCT and whether they received radiation therapy. Life-long follow-up is necessary for survivors to detect, prevent and treat the late endocrine complications in SCT survivors.

Key words: growth disorder, endocrine function, long-term adult survivors

Introduction

Late clinical complications resulting from

intensive treatment for an underlying disease or from conditioning regimen before stem cell transplant (SCT) are a major concern in regard to the quality of life of long-term adult survivors after SCT. Late endocrine complications following SCT in the pediatric patients (1) include thyroid dysfunction (2–5), gonadal dysfunction (6–8) and growth disorder (9–14), most likely due to the effect of irradiation on these endocrine

organs (15, 16). The long-term outcomes of childhood cancer survivors have mainly been investigated by cross-sectional studies (17). Therefore, necessity of a long-term follow-up after SCT was advocated. However, no longitudinal studies investigating growth disorder have been reported to date, and the mechanisms of these endocrine dysfunctions as late complications have not been completely elucidated.

Linear growth is an intricate process affected by several systems including genetic, nutritional and hormonal factors. The intensive treatment related to SCT and these endocrine dysfunctions after SCT may affect all or some of these factors, resulting in decreased growth rate during childhood (18). In particular, irradiation of spinal and long bone cartilage and the epiphyseal growth plate as the target organ may influence growth considerably. In contrast, patients who are conditioned without irradiation regimens, such as with cyclophosphamide (CY) and/or busulfan (Bu), have been reported to grow normally (19, 20). Although several previous studies have confirmed the relationship between growth disorder and SCT, the detailed mechanism for the delay of growth is still not fully understood. The aim of the present study was to investigate the relationships among growth and endocrine functions in long-term adult survivors after childhood SCT at a single institution and to elucidate detailed underlying mechanisms.

Patients and Methods

Patients

We reviewed the clinical records of 215 patients who received allogeneic SCT at Tokai University Hospital between 1982 and 1997. The inclusion criteria of the present study were survival at least 5 yr after SCT and achievement of adult height. Fifty-nine patients (42 males and 17 females) were eligible for this study, and all were older than 15 yr of age at the time of their last visit. Five patients (three Fanconi

anemia, one Gaucher disease and another cancer with delayed bone age before SCT) were excluded from the present study because of pre-existing endocrinological disorders before SCT. The remaining 54 patients (39 males and 15 females) fulfilled the criteria and were included in the present study. At the time of SCT and at the beginning of follow-up, written informed consent was obtained from the patients and/or their parents for the treatment procedure and follow-up after SCT. Patient characteristics are summarized in Table 1.

Transplantation procedure

Conditioning regimens for SCT are shown in Table 1. The conditioning regimens for 48 patients consisted of irradiation combined with/without CY and/or other drugs; 6–12 Gy of total body irradiation (TBI) was given to the malignant disease group in three to six fractions, and 3–10 Gy of thoraco-abdominal irradiation (TAI) was given to the nonmalignant disease group in one to five fractions. The remaining 6 patients received conditioning without irradiation. Prophylaxis against GVHD varied during the time period; methotrexate, cyclosporine or a combination of both drugs were used.

Evaluation of growth and growth hormone secretion

Height measurements were converted to height SDS standardized for age and sex using the reference standards of Japanese, and the growth data of each patient were evaluated by changes in height SDS. A patient was defined to have achieved adult height when the growth velocity became less than 1 cm/yr for two consecutive years. Short stature was defined as an adult height of <2.0 SD. Severe short stature was defined as an adult height of <2.0 SD and changes in height SDS of –2.0 and more. Height and growth velocity data based on the National Survey in Japan in 2000 were used as the reference standard.

GH secretion was repeatedly assessed by

Table 1 Patient characteristics

	All (n=54)	Males (n=39)	Females (n=15)
Age at BMT (yr old)	11.3	11.5	10.0
	0.9–15.0	0.9–15.0	3.4–15.0
Follow-up duration (yr)	8.2	7.8	9.3
	4.0–19.3	4.2–19.3	4.0–14.5
Height at BMT (SDS)	−0.41	−0.40	−0.52
	−2.48–1.93	−2.48–1.27	−1.18–1.93
Final height (SDS)	−1.15	−1.23	−0.98
	−5.43–1.20	−5.43 – 0.46	−2.68–1.20
Age at BMT			
<10 yr	21	14	7
≥10 yr	33	25	8
Primary disease			
Malignant disease	40	27	13
ALL	15	10	5
AML	12	8	4
CML	7	5	2
NHL	5	4	1
Other cancers	1	0	1
Nonmalignant disease	14	12	2
AA	12	10	2
Others	2	2	0
Prior CRT			
CRT(+)	5	4	1
CRT(−)	49	35	14
Conditioning regimen			
Irradiation	48	33	15
TBI ± CY ± other drugs	40	26	14
TAI + CY ± other drugs	8	7	1
No irradiation	6	6	0
CY ± Bu + other drugs	6	6	0

Acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogeous leukemia (CML), non-Hodgikin lymphoma (NHL), aplastic anemia (AA), human leukocyte antigens (HLA), cranial radiotherapy (CRT), total body irradiation (TBI), thoraco-abdominal irradiation (TAI), cyclophosphamide (CY), Busulfan (Bu).

insulin tolerance test before SCT and annually thereafter. Because of a remarkable variation in peak GH response to the insulin tolerance test in each individual, a median of 8 insulin tolerance tests (range 1–12) were performed during the follow-up period and were necessary to make a diagnosis of poor GH response. Regular insulin (0.1 U/kg) was injected intravenously in the morning after an overnight fast, and blood was obtained every 30 min for 120 min via an indwelling venous catheter. GH deficiency was defined as a GH level of <10 ng/mL in response

to stimulation with regular insulin. GH was assayed by either radioimmunoassay or immunoradiometric assay. The plasma IGF-I concentration was determined in extracted plasma by immunoradiometric assay.

Other endocrine functions

In male patients, onset of puberty was defined as a testicular volume of ≥ 4 mL (21). Testicular volume was determined using an orchidometer, as described by Prader (22). Testicular measurement using the orchidometer was performed by a single investigator (S.K.). Testicular Leydig cell function and germinal epithelium damage were evaluated using the basal serum LH levels, basal serum FSH levels and serum testosterone levels. The normal basal serum LH and FSH levels at our institute are <5 mIU/mL and <9 mIU/mL, respectively. Partial Leydig cell dysfunction and partial germinal epithelium damage were defined as increased basal LH and basal FSH levels (>15 mIU/mL and >20 mIU/mL, respectively) with normal testosterone levels. In female patients, the time of the menarche and recurrence of menstruation after BMT were recorded. Ovarian function was evaluated using the basal serum LH levels, basal serum FSH levels and serum E_2 levels after BMT. Primary ovarian failure was defined as an increased basal FSH level (>10 mIU/mL). Thyroid function was evaluated before SCT and annually thereafter by serial measurement of basal serum thyroid stimulating hormone (TSH) levels, serum free triiodothyronine (FT3) levels and free thyroxine (FT4) levels. The normal values at our hospital are: 0.30–4.00 μU/mL for TSH, 2.50–4.50 pg/mL for FT3, and 0.75–1.75 ng/dL for FT4. Subclinical compensated hypothyroidism was defined as elevated THS levels (4–10 μU/mL) with normal FT4 levels and no clinical symptoms. All measurements were performed in the central laboratory of our hospital. Endocrine tests were basically conducted in the morning fasting state to avoid diurnal variation of hormones.

Bone age

Bone age was assessed for bone maturation by the Tanner and Whitehouse (TW2) method modified for Japanese patients. Seventy-three bone age radiographs obtained at our institution between 1986 and 2002 were evaluated by two pediatric endocrinologists (H.I and Y.T). Because bone age evaluation can be influenced by related clinical information and by individual experiences, intrapersonal and interpersonal variation was assessed as follows. One pediatric endocrinologist (H.I) first evaluated bone age by chronological age order after familiarizing himself with the patient information; then evaluated bone age blindly in random order. The other pediatric endocrinologist (Y.T) read bone age blindly in by random order only. The three sets of results were analyzed by a statistical method for agreement degree. Completion of bone maturity was defined as a bone age of 17.0 yr in males and 15.3 yr in females according to the TW2 method modified for Japanese patients.

Statistical analysis

Medians and ranges are used throughout the text, tables and figures because the distribution of the data was skewed. The Wilcoxon signed rank test was used to compare the changes in height SDS before and after SCT. The Mann-Whitney U-test was used to compare the differences between groups. The Chi-square and Fisher's exact probability tests were used to assess the association between endocrine dysfunction and particular clinical features. Spearman's correlation coefficient by rank was used to examine the relation between two variables. This statistical analysis was carried out using the GraphPad PRISM statistical package. A p value of less than 0.05 was considered statistically significant.

Results

Changes in growth among patients who achieved adult height

We focused on changes in growth according to the type of conditioning regimen for SCT and several other factors associated with SCT. The changes in height SDS of the patients who reached their final heights showed that the adult height SDS was significantly decreased (median −1.15, range −5.43 to 1.20) compared with the height SDS at SCT (median −0.41, range −2.84 to 1.93, $p<0.001$; Fig. 1A). According to sex, the changes in height SDS also indicated that the adult height SDS was significantly decreased (median −1.23 and range −5.43 to 1.20 for males; median −0.98 and range −2.68 to 0.66 for females) compared with the height SDS at SCT in both sexes (median −0.21 and range −2.48 to 1.27 for males; median −0.51 and range −1.18 to 1.93 for females; $p<0.05$). Therefore, the SCT procedure was considered to have caused growth disorder in these patients.

The difference in growth outcome according to age at SCT indicated that patients who received SCT before 10 yr of age (9 yr of age or younger) showed significantly greater reductions in height SDS (median −1.75, range −4.80 to −0.10) compared with those who received SCT at or after 10 years of age (median −0.50, range −1.74 to −1.20; $p<0.001$; Fig. 1B). We also analyzed whether the difference in linear growth depends on the type of conditioning regimen including irradiation. In regard to the mode of irradiation, patients who received irradiation experienced a significantly greater decrease in adult height SDS (median −1.01, range −4.80 to 0.74) compared with those who received only chemotherapy (median −0.31, range −0.83 to 1.20; $p<0.05$; Fig. 1C). Although eight patients were treated with cranial irradiation prior to SCT, the changes in height SDS did not indicate any differences in these patients compared with those who did not receive cranial irradiation. Furthermore no statistical differences were observed regarding
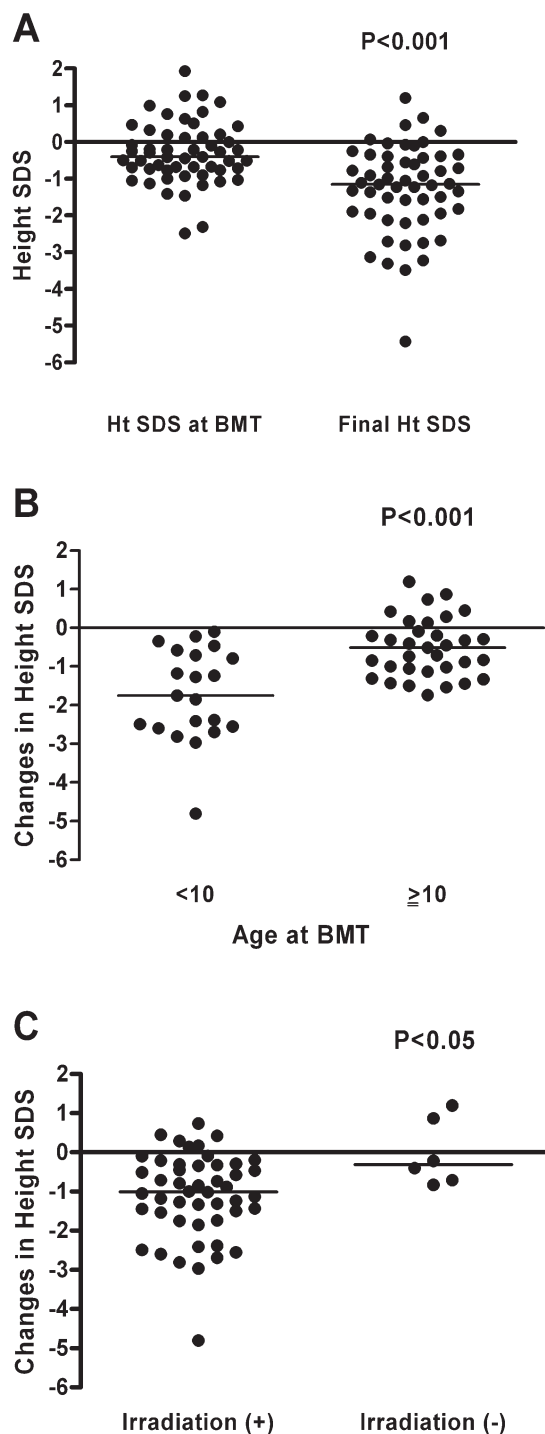

Fig. 1 Individual changes in height SDS at SCT and adult height SDS (A), changes in height SDS by age at SCT (B) and changes in height SDS by type of conditioning regimen (C).
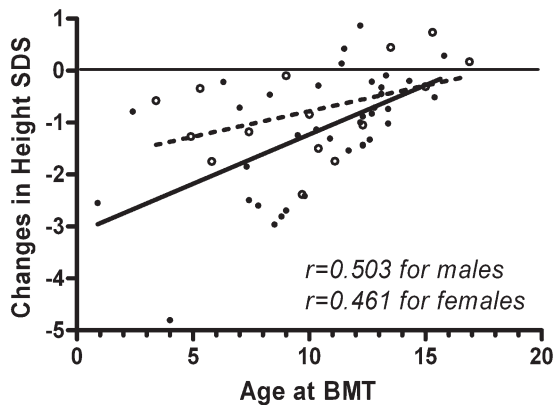
Fig. 2 Changes in height SDS by age at SCT in males and females. As a whole, the mean loss of height in all patients who received SCT during childhood was estimated to be approximately 1 SDS/6.5 yr (r=0.517). The solid line and closed circle indicate male patients, and the dotted line and open circle indicate female patients.

primary disease. Fifteen patients (2 in female) were treated with glucocorticoid hormone for treatment of chronic GVHD. However, no statistically significant difference in adult height was observed in regard to glucocorticoid hormone treatment.

A 4-yr-old boy with severe aplastic anemia received SCT twice. His conditioning regimens consisted of TAI + cyclophosphamide + antilymphocyte globulin for the first SCT and no conditioning regimen for the second SCT. His height at SCT was 98.0 cm (–0.63 SD), and his adult height was 145 cm (–5.43 SD) with a well-proportioned stature. He did not experience GVHD. This serum IGF-I levels remained in the lower half of the normal range, and an insulin tolerance test indicated a normal pattern of GH secretion throughout the follow-up period. Although his bilateral testicular size was 10 mL, his serum testosterone levels remained in the lower half of the normal range.

The changes in height SDS were re-sorted by age at SCT for a more detailed analysis.

Performance of SCT at a young age was a strong risk factor for development of growth reduction compared with performance at an older age (Fig. 2). This early age effect was more pronounced in males than in females. As a whole, the mean loss of height in all patients who received childhood SCT was estimated to be approximately 1 SDS/6.5 yr (r=0.517). Age at the time of transplantation has a strong influence on height SDS after SCT.

Changes in GH secretion after SCT

GH secretion was evaluated by insulin tolerance test and serum IGF-I levels in 54 patients before SCT and annually thereafter. Fourteen patients experienced poor GH secretion (GH level of <10 ng/mL) at least twice, although permanent GH deficiency was not observed. Serum IGF-I levels also remained in the lower half of the normal range throughout the follow-up period (Fig. 3), although five patients had transiently low serum IGF-I levels at least once. There were no statistical differences between patients with poor (median –0.95, range –2.81 to 0.74) or appropriate GH responses (median –0.86, range –4.80 to 0.87; p=0.765) or between patients with low (median –2.27, range –2.81 to 0.42) or normal IGF-I levels (median –0.84, range –4.80 to 0.87; p=0.184). GH replacement therapy was not performed in these patients after SCT because the poor GH secretion was transient.

Other endocrine functions

We examined the relationships among growth and endocrine functions during the pubertal period. All patients had adult genitalia (Tanner stage V) at the last evaluation. In the male patients, puberty started spontaneously in all patients in accordance with the increase in testicular volume (≥4 mL). In all but three patients (UPN 1, 18 and 120), the serum testosterone level reached an adult level at some points after SCT (Fig. 4C). All patients, however, experienced increased basal LH and FSH levels with normal serum testosterone levels as they
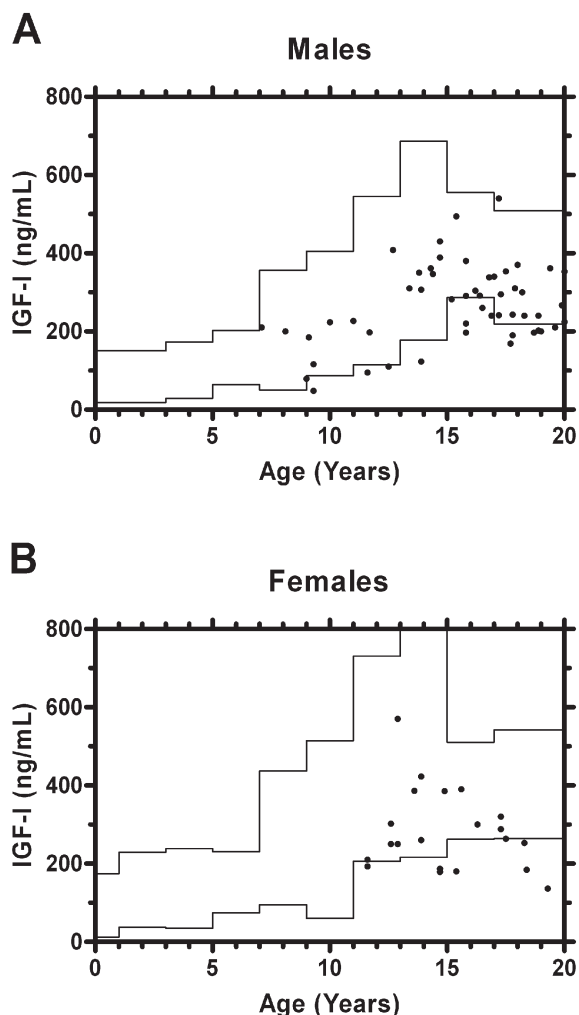
A

Males

B

Females

Fig. 3 Changes in IGF-I. The upper part represents males (A), and the lower part represents females (B).

approached adolescence, indicating the presence of partial Leydig cell dysfunction and partial damage of the testicular germinal epithelium at some time during the follow-up period, respectively (Figs. 4A and 4B).

In female patients who received SCT before 10 years of age, all seven patients who had not manifested menarche before SCT entered puberty spontaneously and experienced menarche after SCT at a median age of 13.5 yr (range 12.8 to 14.5 yr) which is appropriate for healthy Japanese girls. They also had sustained rises in their

gonadotropin levels before menarche (Figs. 4F and 4G). Their serum FSH levels, however, decreased towards the normal range after menarche. All patients who received SCT before 10 yr of age had normal E2 levels during the pubertal period without hormone replacement therapy (Fig. 4H), although partial ovarian failure was observed in all patients. On the other hand, 2 of the 8 patients who received SCT at or after 10 yr of age spontaneously manifested menarche after SCT. The remaining six patients were diagnosed as having primary gonadal dysfunction after SCT. Although three patients started hormone replacement therapy due to clinical symptoms of gonadal dysfunction, two other patients did not accept hormone replacement therapy for various reasons.

In regard to thyroid function, subclinical compensated hypothyroidism was observed during the post-SCT period in all patients (Figs. 4D and 4E for males and Figs. 4I and 4J for females). Because they had no clinical symptoms, we did not treat them with levo-thyroxin. Thus, the peripheral hormone concentration acting on the target organs was appropriate for the pubertal age.

Bone age

The bone age scores of the pediatric endocrinologist who evaluated bone age in chronological order after familiarizing himself with the patient information and those of the other pediatric endocrinologist who evaluated bone age in random order were statistically correlated by Spearman correlation (r=1.0). The bone ages determined by the two endocrinologist without the use of patient information were also statistically correlated (r=0.968, p<0.001). Therefore, we utilized the later readings for evaluation of bone age in the present study.

We examined bone age in 21 patients (14 males and 7 females) to investigate the causes of growth disorder in patients who received SCT before 10 yr of age (Table 1). Bone age tended to be delayed in females than in males, although
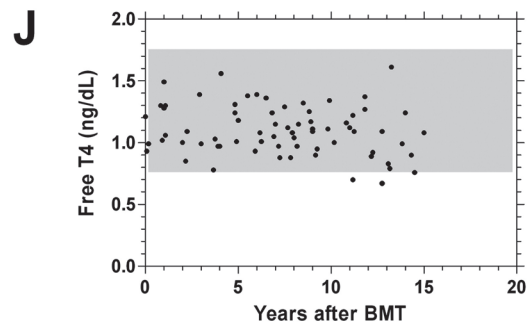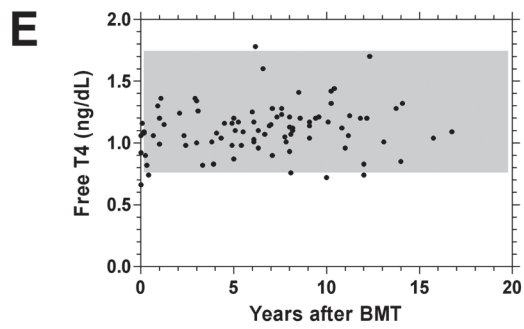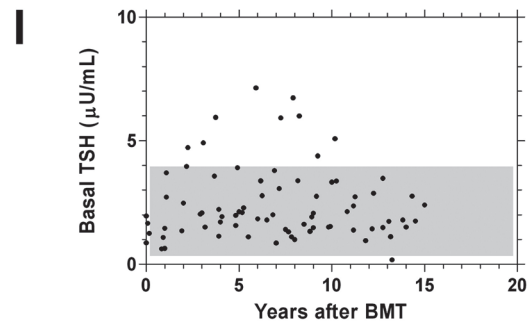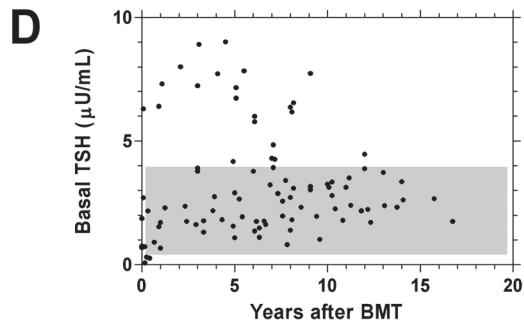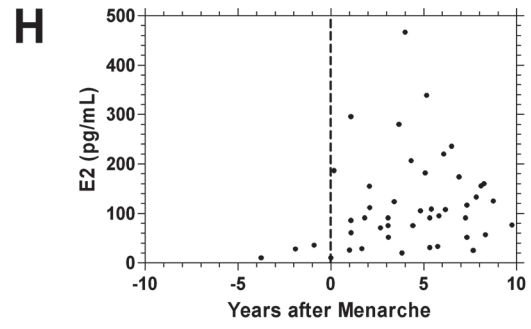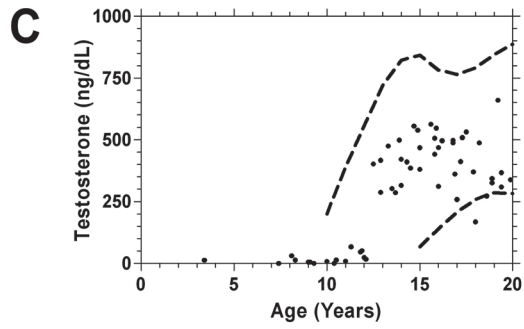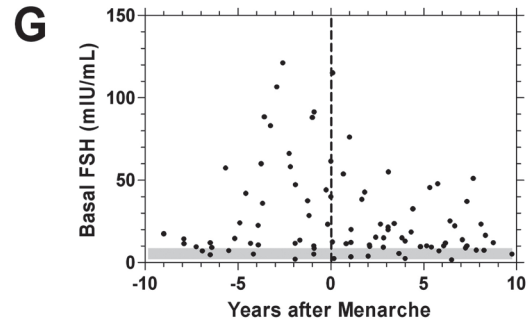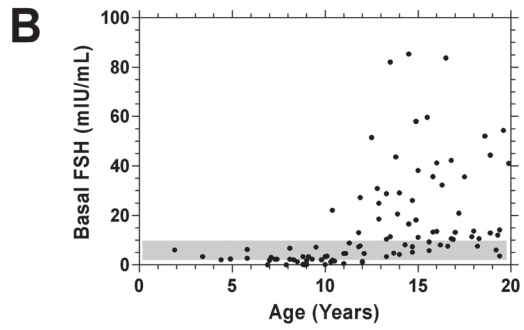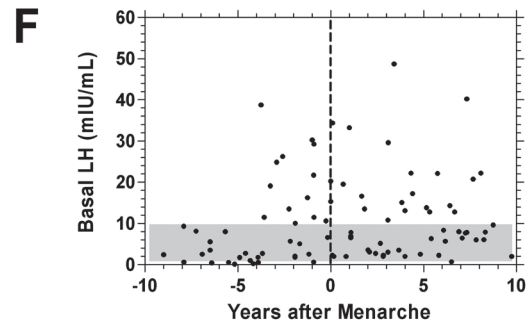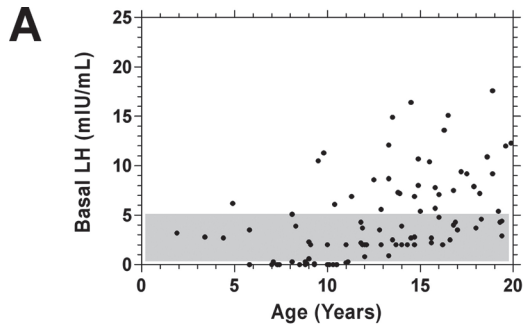
the difference was not statistically significant. No differences regarding type of conditioning regimen, including irradiation, were observed. According to the endocrine function test, these patients did not exhibit endocrine dysfunctions, including permanent GH deficiency and precocious puberty. Therefore, bone maturity did not contribute as a cause of growth disorder in this series.

Individual growth curves after SCT

Among the 39 male patients, 8 of the 14 patients who received SCT before 10 yr of age were found to have a severely short stature, while no similar effect was found for the 25 patients who received SCT at or after 10 yr of age (p<0.001). On the other hand, among the 15 female patients, only 1 of the 7 patients transplanted before 10 yr of age was found to have a severely short stature. Therefore, the presence of severely short stature was more pronounced in males than females. Individual growth curves after SCT were evaluated in order to clarify the details of growth dynamics and growth disorder. According to longitudinal growth curves plotted on cross-sectional growth charts, the male individual growth curves indicated that a significant growth spurt was not observed during the pubertal period in patients who received SCT before 10 yr of age compared with those who received SCT at or after 10 yr of age (Figs. 5A and 5D). Patients who received SCT before 10 yr of age tended to experience extreme decreases in changes in height SDS (median –2.5, range –4.8 to –0.2) compared with those who received SCT at or after 10 yr of age (median –0.8, range –1.5 to 0.9; p<0.01; Figs. 5B and 5E). No statistical differences were observed in growth velocity SDS in patients who received SCT before 10 yr of age (median –1.2, range –6.9 to –2.6) and those who received

SCT at or after 10 yr of age (median –3.6, range –6.7 to 3.5; p=0.315). The growth velocities of patients who received SCT before 10 yr of age, however, dramatically decreased in the pubertal period compared with patients who received SCT at or after 10 yr of age (Figs. 5C and 5F) begining two years after SCT. In female patients, individual growth curves and growth velocity indicated loss of growth spurt during the pubertal period in patients regardless of age at SCT (Fig. 6).

Discussion

Growth disorder is one of the significant late complications among long-term survivors following SCT. The results of this study show that loss of growth spurt, which caused short stature after SCT, was observed during the pubertal period, but that it was not associated with endocrine functions, especially GH secretion, or IGF-I levels and bone maturation. The retardation of spinal and long bone growth caused by irradiation is thought to be closely related to impairment of growth during the pubertal period.

The adult height achievements and decreased growth of patients who have received SCT during childhood have previously been reported (19, 23, 24), and the mean loss of height has been estimated to be approximately 1 height SDS compared with the mean height at the time of SCT (13, 14, 25). Our results, which showed a difference between the height SDSs before and after SCT of –0.76 SDS, are in agreement with this previously accumulated data. Therefore, SCT has a great influence on growth convalescence in patients who receive SCT during childhood. Sanders (26) also observed a greater impact of age on adult height in 15 children who were less

Fig. 4   Changes in endocrine function. The left and right rows indicate endocrine function in male and female patients, respectively. The top rows represent the basal LH and FSH levels. The middle rows represent the testosterone and estradiol levels in the males and females, respectively. The two bottom rows represent the basal TSH and free T4 levels. The shaded areas indicate the normal ranges.
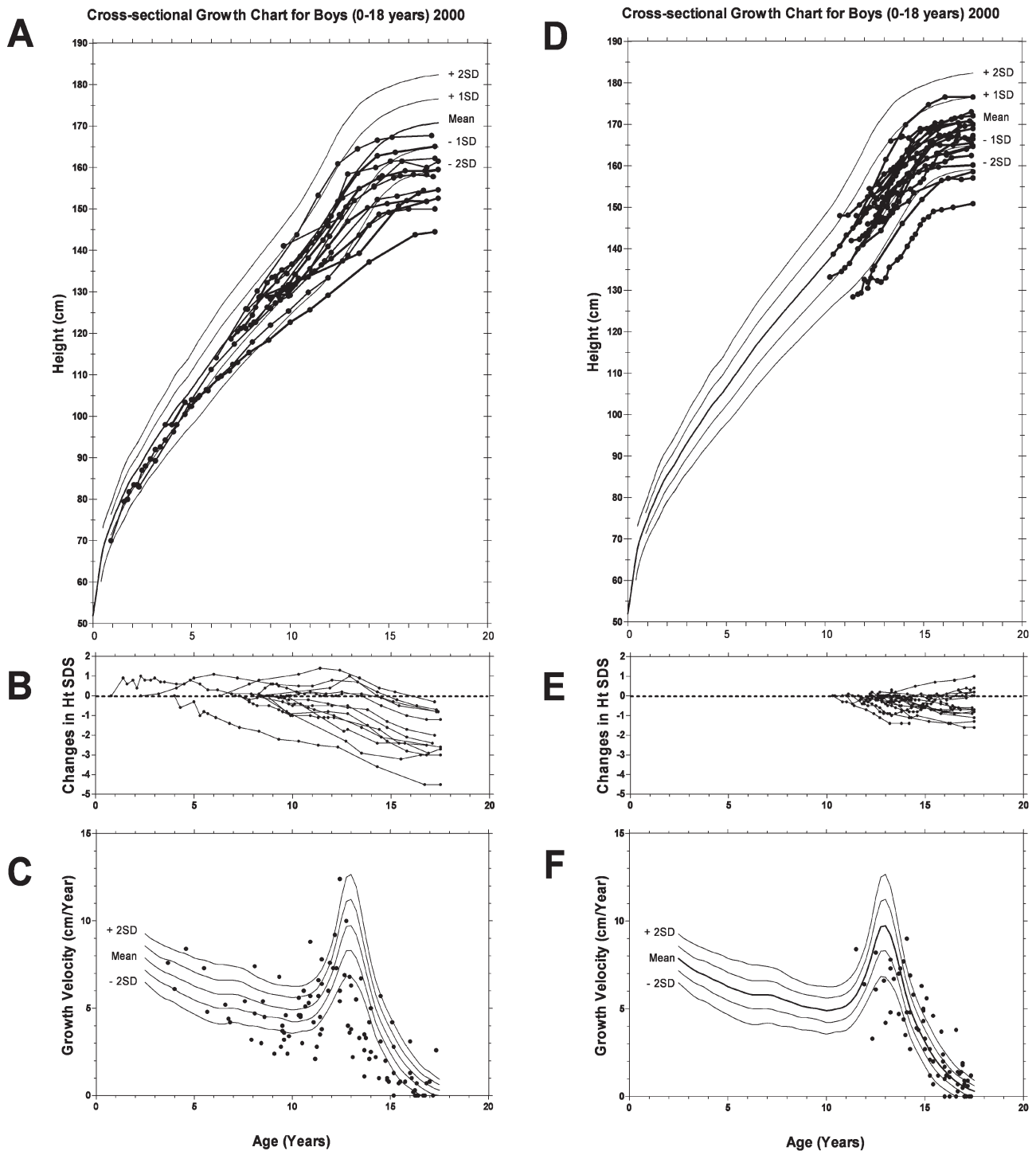
Fig. 5 Individual longitudinal growth curves after SCT in males. The upper figures represent individual longitudinal growth curves plotted against cross-sectional growth charts. The middle figures represent changes in height SDS. The lower figures represent growth velocity in the following year after SCT. The left figures represent male patients who received SCT before 10 yr of age and the right figures represent male patients who received SCT at or after 10 yr of age. Connecting lines represent data from individuals.
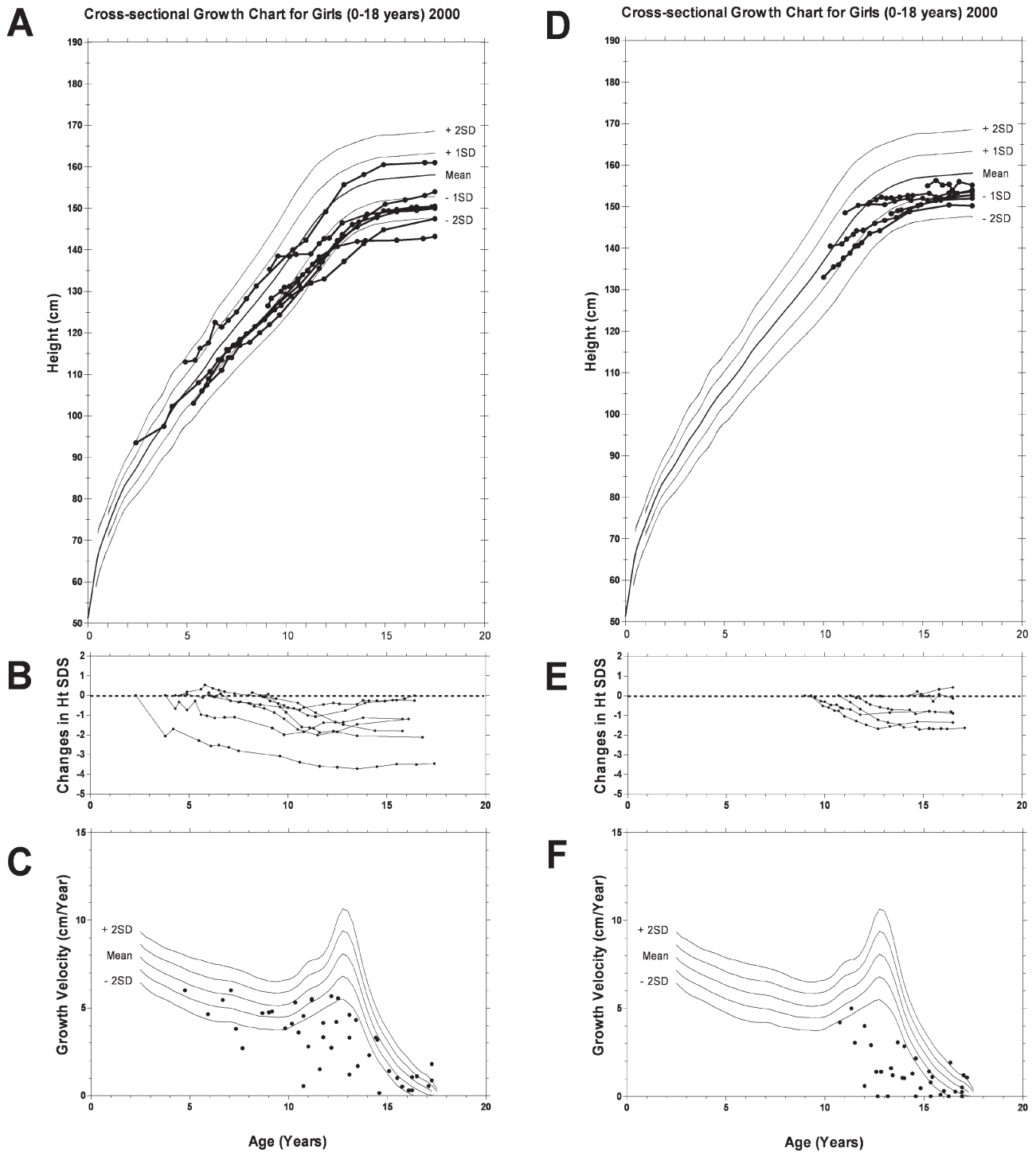
Fig. 6 Individual longitudinal growth curves after SCT in females. The upper figures represent individual longitudinal growth curves plotted against cross-sectional growth charts. The middle figures represent changes in height SDS. The lower figures represent growth velocity in the following year after SCT. The left figures represent for female patients who received SCT before 10 yr of age and the right figures represent female patients who received SCT at or after 10 yr old. Connecting lines represent data from individuals.

than 6-years of age at the time of SCT, which the mean adult height was –3.49 SD (±1.77). On the other hand, in 93 children receiving transplants between 12 and 15 years of age, the mean adult height was –0.37 SD (±1.38). Age at the time of SCT, therefore, is the most important factor when dealing with toxic late-effects in long-term survivors, and our results agree with this previous report.

Growth disorder is more pronounced in patients who receive SCT at a younger age and in those who receive irradiation. In contrast, patients who are conditioned with non-TBI regimens usually grow normally. Holm et al. reported an increased tendency of loss of adult height among children who received TBI at younger ages (27). Their finding is similar to our experiences with patients who have received TBI; they tended to experience a greater decrease in adult height SDS. The decrease in growth found in the irradiated group cannot be explained by impaired secretion of GH because TAI spares the hypothalamus and pituitary gland. The reduction in growth rate observed in the irradiated group, therefore, may be explained by the direct effect of irradiation on the spinal and long bone cartilage and epiphyses. TAI has an influence on spinal epiphysis and proximal epiphyses of the femoral bones, while TBI affects to whole body, including spinal and long bone epiphyses. Our data indicated that the changes in height SDS (median age at SCT) were –0.94 SDS (11.6 yr of age), –1.20 (7.9) and –0.31 (11.4) in the patients who received TBI, TAI and chemotherapy alone, respectively. According to our results, which showed a mean loss of height of approximately 1 SDS/6.5 yr in all patients who received SCT during childhood, the actual changes in height SDS in the patients who received TAI may be –0.57 because of the younger age at SCT of the patients who received TAI among the two remaining groups. Patients who received TAI, therefore, tended to experience a smaller reduction in adult height SDS compared with patients who received TBI. According to

the growth charts, the individual growth curves indicated that loss of growth spurt occurred in patients who received SCT before 10 yr of age during the pubertal period; Brauner et al. also reported that continuous growth failure due to irradiation was indicated in the defective longitudinal bone growth (28). Therefore, irradiation strongly affects longitudinal growth in patients who receive SCT.

It is well known that growth plate cartilage located mainly in the spinal and long bones is sensitive to irradiation. Many studies have suggested a close correlation between irradiation damage to growth plate cartilage and retardation of skeletal growth. Irradiation influences not only cell replication but also organization of the cartilage matrix and transition from cartilage to bone. Bakker et al. reported an in vivo study in the rat in which radiation resulted in growth delay and disorganization of the columnar structure of the growth plate, which could indicate impaired synchronization of the process of proliferation and differentiation in the growth plate (29). They suggested that growth delay is persistent and that there is certainly loss of growth spurt in the rat model. This is in line with the human situation after SCT, where damage to the growth plates also results in persistent growth retardation. If all epiphyses were damaged equally, the relative loss of growth potential should be equal at every epiphysis. There are a greater number of epiphyses per unit surface area in patients who receive TBI than in patients who receive TAI, and cumulative loss of growth may be a possible explanation in the patients who receive TBI. Although our preliminary data indicates that the sitting height / standing height ratios were not different among the groups, further clinical investigation and animal studies are required to clarify the underlying mechanism to elucidate this point.

In the present study, the change in height SDS was greater in boys compared with girls (–1.01 SDS in boys vs –0.47 SDS in girls). In addition, in boys, most of the decrease in height

SDS occurred during puberty, whereas in girls, the decrease in height SDS was slightly greater before puberty and much less during puberty. There are several possible explanations for these differences between boys and girls. First, the time between SCT and age at adult height was slightly greater in girls (median 9.3 yr vs 7.8 yr in boys). Furthermore, growth velocity is greater in healthy boys compared with girls; limiting growth velocity may have had a greater effect on boys. Finally, ovarian failure frequently occurred in the girls, whereas all but three male patients had serum testosterone levels that reached an adult level at some point after SCT. Delayed introduction of sex hormone replacement therapy in girls may have resulted in a prolonged period of prepubertal growth.

Our study indicated that growth disorder after SCT was influenced mainly by age at SCT, irradiation as a conditioning regimen and loss of growth spurt during the pubertal period without GH deficiency. We, therefore, recommended that long-term survivors who have received SCT in childhood deserve life-long attention to detect, prevent and treat symptoms and disorders of endocrine function.

Acknowledgment

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