学位論文

Advantages and limitations of estrogen replacement therapy on hypogonadal survivors of childhood cancer
（小児がんサバイバーにおける性腺機能低下症に対するエストロゲン補充療法の有益性と限界）

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ORIGINAL ARTICLE

Advantages and limitations of estrogen replacement therapy on hypogonadal survivors of childhood cancer

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Abstract

Background Hypogonadism is a significant late complication in childhood cancer survivors (CCS). The aim of this study was to elucidate the advantages and limitations of estrogen replacement therapy (ERT) for CCS with hypogonadism.

Methods Seventeen CCS were divided into two groups: gonadal hypogonadism (GH) group (n = 8) and central hypogonadism (CH) group (n = 9). Pearson correlation coefficients were used to investigate the impact of cancer management on final height, bone density, and uterine development.

Results Seven of GH group had hematologic malignancies, and all of them underwent total body irradiation before bone marrow transplantation. The GH group showed significant positive correlations between the onset age of disease treatment and final height ($p < 0.05$, $R = 0.712$) and uterine size following ERT ($p < 0.05$, $R = 0.775$). All CCS in the CH group had brain tumors, and seven of them received chemotherapy. There were trends towards positive and negative correlations between the onset age of disease treatment and final height ($p = 0.09$, $R = 0.598$) or uterine size ($p = 0.07$, $R = -0.669$), respectively. A negative correlation trend was observed between the age at ERT initiation and final height ($p = 0.07$, $R = -0.769$) or bone density ($p = 0.18$, $R = -0.626$) in six CH patients who received growth hormone therapy. Five CCS in both groups experienced osteoporosis, despite receiving ERT.

Conclusion Individualized management strategies beyond ERT are essential to reduce long-term complications in CCS with hypogonadism, considering the type and timing of cancer treatment.

Keywords Childhood cancer survivors · Estrogen replacement therapy · Growth hormone therapy · Hypogonadism · Short stature · Uterine size · Osteoporosis

Introduction

Childhood cancer survivors (CCS) are at risk of both short- and long-term complications, including endocrinological abnormalities, with hypogonadism being one of the most significant issues [1, 2]. Long-term estrogen deficiency resulting from hypogonadism can significantly impair quality of life by affecting height growth, peak bone mass acquisition, and fertility [3–5]. In 2007, the concept of oncofertility, which seeks to achieve simultaneous cancer treatment and fertility preservation, was introduced by Woodruff TK [6]. Subsequently, comprehensive information pertaining to treatment-related gonadal toxicity and suitable reproductive healthcare has been spread to pediatric and adolescent-young adult cancer patients and health care providers worldwide. Despite these endeavors, female survivors of childhood cancer still suffer from a range of complications, such as short stature, osteoporosis, and infertility.

The importance of estrogen replacement therapy (ERT) for hypogonadal women who have survived childhood cancer is widely acknowledged. Nevertheless, there exists a paucity of consensus on the optimal approach to administering ERT to this population [7], and a considerable number of patients continue to exhibit suboptimal outcomes such as

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short stature, osteoporosis, or inadequate uterine growth despite undergoing ERT. Therefore, the aim of this study was to elucidate the benefits and limitations of ERT for hypogonadal women who have survived childhood cancer.

Materials and methods

Patients

This study included women who had survived childhood cancer from birth to 14 years of age and were managed at Kumamoto University Hospital for amenorrhea between January 2018 and October 2022. Electronic medical records were accessed to identify patients who received ERT, with exclusion criteria applied to those who experienced withdrawal bleeding after a progesterone challenge test, had not reached final height, or were lost to follow-up.

The women included in this study were divided into two groups: gonadal hypogonadism (GH) and central hypogonadism (CH), in accordance with the diagnostic criteria for premature menopause established by Rebar et al. [8]. Diagnosis of GH was based on measuring serum follicle-stimulating hormone (FSH) levels after withdrawal bleeding, with FSH levels greater than 40 mIU/mL considered indicative of GH. Additionally, serum anti-mullerian hormone (AMH) levels were measured when FSH levels were 40 mIU/mL or less. Women with AMH levels below the sensitivity threshold (0.03 ng/mL) were also categorized as GH. On the other hand, women with FSH levels of 40 mIU/mL or less and AMH levels of 0.03 ng/mL or higher were placed in the CH group.

Retrospective analysis of electronic medical records was conducted to extract relevant data on patients' clinical characteristics, primary disease and its treatment, endocrine findings, height, vertebral bone mass, and changes in uterine size. This study was approved by Kumamoto University Hospital's Ethics Committee (Ethics No. 2135).

Estrogen replacement therapy

A long-term ERT regimen was administered to female survivors of childhood cancer presenting with amenorrhea. Initially, conjugated equine estrogen (PREMARIN TABLETS®, Pfizer Inc., USA) was administered at a daily dose of 0.3125 mg, which was gradually increased to 0.625 mg and 1.25 mg every 6 to 12 months. Thereafter, a transdermal extended-release estradiol formulation (Estrana Tape®, Hisamitsu Pharmaceutical Co., Ltd., Japan) was introduced in 2000, replacing conjugated equine estrogen. The lowest dose of transdermal estradiol was initiated at 0.09 mg every 2 days and increased gradually to 0.18 mg, 0.36 mg, and 0.72 mg every 6 to 12 months. Throughout the treatment period, the height, bone mineral density, and blood levels of estradiol, luteinizing hormone, and FSH were monitored. The doses of both conjugated equine estrogen and transdermal extended-release estradiol formulations were gradually increased based on these parameters over a period of 2–3 years [9], until the height growth ceased or the epiphyseal line closed. Once this occurred, estrogen-progestogen therapy was initiated, involving Estrana Tape® administered every 2 days at a dose of 0.72 mg, along with C-21 progestins, such as dydrogesterone (10 mg per day) or chlormadinone acetate (4 mg per day).

Vertebral bone mass

Vertebral bone mass was assessed at the L2-L4 levels using dual-energy X-ray absorptiometry (DXA) with the Discovery DXA system (Hologic, Inc., Japan). The diagnostic criterion for low bone mass was defined as less than 0.809 g/m^2, which corresponds to less than 80% of the Young Adult Mean, in accordance with the diagnostic criteria of primary osteoporosis in Japanese girls [10]. In cases where bone mass was measured multiple times, the latest measurement was used for analysis.

Uterine size

To assess uterine development, sagittal cross-sectional images of the uterus were obtained using abdominal or transvaginal ultrasonography. The cross-sectional area was determined by measuring the uterine long diameter (d1) and the maximum anterior–posterior diameter of the uterine body (d2) through application of the ellipse formula ($d1/2 \times d2/2 \times \pi$). When uterine cross-sectional area was measured multiple times, the oldest and newest values were selected. Poor responsiveness to estrogen was defined as a growth rate less than 1, which was determined by dividing the latest value of uterine cross-sectional area by the pre-treatment value before ERT initiation. In the CH group, four women lacked data on uterine area before the start of ERT, and one lacked information on uterine area after the start of ERT.

Statistical analyses

Statistical analysis was conducted using the Statistical Package for the Social Sciences software version 24 (IBM, SPSS Statistics, USA). Pearson correlation coefficients were used to determine the strength of the association between two variables.

Results

Patient characteristics

During the study period, a total of 24 CCS experienced amenorrhea. Among these, 17 individuals met the eligibility criteria for analysis (Fig. 1) and are presented in Table 1. The GH group comprised 8 patients and the CH group comprised 9 patients, with a median age at first treatment for the primary disease of 7.9 years (range: 0.4 to 14.4 years) in the GH group and 7.0 years (range: 1.0 to 14.8 years) in the CH group. Among the GH group, leukemia was the primary disease in 5 out of 8 patients, with 7 out of 8 patients receiving hematopoietic stem cell transplantation prior to total body irradiation (TBI). Only one patient in the GH group had a brain tumor and received growth hormone therapy at the age of 9 years. In contrast, all patients in the CH group had a brain tumor, with 6 out of 9 patients initiating growth hormone therapy at a median age of 9.5 years (range: 5.2 to 13.9 years).

Estrogen replacement therapy

In the GH and CH groups, the median age at which ERT was initiated was 14.8 (range: 10.0 to 18.5 years) and 14.3 years (range 10.0–17.5 years), respectively, with 70.6% of CCS not commencing ERT until the age of 12 (Table 2). The median interval between the start of primary disease management and the initiation of ERT was 7.7 and 6.7 years in the GH and CH groups, respectively. The median age at which the first withdrawal bleeds occurred following the termination of height gain or closure of the epiphyseal line and subsequent administration of estrogen-progestogen therapy was 17.8 and 15.8 years in the GH and CH groups, respectively. Only one patient in the GH group did not experience withdrawal bleeding for several years, after which it resumed.

Final height

The median age at final height assessment was 22.2 years in the GH group and 18.7 years in the CH group, with corresponding mean heights of 151.2 cm and 152.5 cm, respectively, as presented in Table 2. Among the 17 CCS, five (67.5%) in the GH group and three (33.3%) in the CH group had a final height of 150 cm or below, which represents the -1.5 standard deviation from the mean height of 158 cm for 17-year-old Japanese women [11].

The study explored the relationship between patients' age at treatment for the primary disease or ERT and their height. In the GH group, a significant positive correlation was observed between final height and age at initiation of treatment for the primary disease ($p < 0.05$, $R = 0.712$). The CH group also showed a similar trend, although not statistically significant ($p = 0.09$, $R = 0.598$), as shown in Fig. 2A. Further, the correlation between age at ERT initiation and final height was investigated (Fig. 2B). The correlation coefficient was positive in the GH group, although not significant

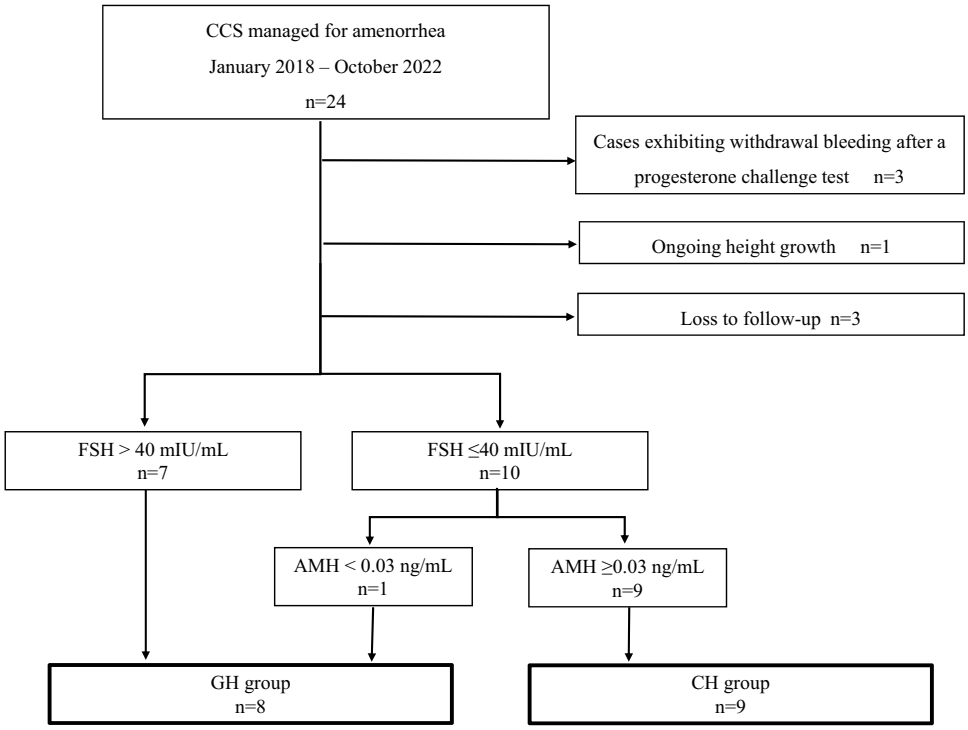

Fig. 1 Selection criteria flowchart for retrospective cohort. *AMH* anti-Mullerian hormone, *CCS* childhood cancer survivors, *CH* Central hypogonadism, *FSH* follicle stimulating hormone, *GH* Gonadal hypogonadism

Table 1 Clinical characteristics

	Gonadal hypogonadism (GH) (n = 8)	Central hypogonadism (CH) (n = 9)
Age at initiation of primary disease treatment, years, median (range)	7.9 (0.4–14.4)	7.0 (1.0–14.8)
Primary disease, *n* (%)		
Leukemia[a]	5 (67.5)	0
Malignant lymphoma	1 (12.5)	0
Neuroblastoma	1 (12.5)	0
Brain tumor	1 (12.5)	9 (100)
Primary disease treatment, *n* (%)		
Chemotherapy with HSCT[b]	7 (87.5)	0
Surgery	0	2 (22.2)
Surgery, chemotherapy, and radiation therapy to brain	1 (12.5)	3 (33.4)
Chemotherapy and radiation therapy to brain	0	4 (44.4)
Growth hormone treatment		
Received, *n* (%)	1 (12.5)	6 (66.6)
Age at initiation, years, median (range)	9.0	9.5 (5.2–13.9)
Not received, n (%)	7 (87.5)	3 (33.4)
Endocrine status at first visit[c]		
Serum FSH, mIU/mL, median (range)	84.2 (< 0.1–138.4)	0.7 (< 0.1–7.2)
AMH, ng/mL, median (range)	< 0.03	2.10 (0.87—8.78)

AMH anti-Mullerian hormone, *FSH* follicle stimulating hormone, *HSCT* hematopoietic stem cell transplantation

[a]Consisted of acute lymphocytic leukemia (n = 2), acute myeloid leukemia (n = 2), and myelodysplastic syndrome (n = 1)

[b]Included total body irradiation as part of the transplant conditioning regimen

[c]In the GH group, solely one woman demonstrated serum concentrations of both FSH and AMH that were below the level of detection sensitivity of the assay implemented

($p = 0.37$, $R = 0.366$). In contrast, in the CH group, the correlation coefficient displayed a negative trend, albeit not statistically significant ($p = 0.59$, $R = -0.208$). Notably, in six CH patients who received growth hormone therapy, this negative correlation trend between the age at ERT initiation and final height was particularly pronounced ($p = 0.07$, $R = -0.769$). Finally, we investigated the correlation between the duration between the initiation of treatment for the primary disease and the onset of ERT and the final height. As displayed in Fig. 2C, a significant negative correlation was observed in both the GH group ($p < 0.001$, $R = -0.954$) and the CH group ($p < 0.05$, $R = -0.678$).

Bone mineral density

The median age at the time of evaluation was 20.0 years in the GH group and 21.1 years in the CH group, with corresponding mean vertebral bone mass of 0.825 g/cm2 and 0.905 g/cm^2, respectively (Table 2). In the GH group, three out of eight (37.5%) women and in the CH group, two out of nine (22.2%) women had osteoporosis despite receiving ERT.

The study investigated the associations between bone mineral density and the age at initiation of treatment for the primary disease (Fig. 3A), the age at initiation of ERT (Fig. 3B), and the duration from the initiation of treatment for the primary disease to the initiation of ERT (Fig. 3C). There were no significant correlations observed in either the GH or CH groups. However, in six cases of the CH group who received treatment with growth hormone, a negative correlation trend was observed between bone density and age at ERT initiation ($p = 0.18$, $R = -0.626$). Osteoporosis was not exclusively observed in instances where the primary disease was treated at an exceptionally young age (Fig. 3A) or the initiation of ERT was delayed (Fig. 3B).

Uterine development

Table 2 presents the outcomes of the uterine size assessment in response to ERT. In the GH group, the median age at

Table 2 Effects of estrogen hormone replacement on final height, bone mineral density, and uterine size

	Gonadal hypogonadism (GH) (n = 8)	Central hypogonadism (CH) (n = 9)
Age at commencement of ERT, years, median (range)	14.8 (10.0–18.5)	14.3 (10.0–17.5)
≤ 12 years old, n (%)	3 (37.5)	2 (22.2)
> 12 years old, n (%)	5 (62.5)	7 (77.8)
Interval between onset of primary disease treatment and start of ERT, years, median (range)	7. 7 (1.5–10.3)	6.7 (0.5–13.9)
First withdrawal bleeds after estrogen-progestogen therapy, years, median, range	17.8 (15.9–18.9)	15.8 (12.7–17.5)
Final height, cm, mean ± SD	151.2 ± 8.2	152.5 ± 6.8
Age at final assessment, years, median (range)	22.2 (17.7–28.9)	18.7 (16.7–25.5)
Short stature (≤ 150 cm)[a], n (%)	5 (67.5)	3 (33.3)
Vertebral bone mass, g/cm^2, mean ± SD	0.825 ± 0.129	0.905 ± 0.122
Age at last evaluation, years, median (range)	20.0 (16.7–34.5)	21.1 (17.2–26.3)
Osteoporosis, n (%)	3 (37.5)	2 (22.2)
Uterine size[b]		
Age at last evaluation, years, median (range)	23.4 (17.7–34.5)	25.8 (17.2–34.8)
Before ERT, cm^2, mean ± SD	8.7 ± 3.8	9.7 ± 5.6
After ERT, cm^2, mean ± SD	10.2 ± 5.6	14.7 ± 5.2
Observation period, years, median (range)	5.4 (0.4–7.9)	5.3 (1.6–9.1)
Growth rate, %, mean ± SD	134.9 ± 77.9	220.9 ± 199.7
Poor uterine response, n (%)	5 (62.5)	2 (40.0)

ERT estrogen replacement therapy, *SD* standard deviation

[a]Short stature is defined as a height that is at least 1.5 standard deviations below the mean of 17-year-old Japanese women

[b]Four women in the CH group were missing uterine area data before ERT initiation, and one woman was missing data on uterine area after ERT initiation

which uterine size was last evaluated was 23.4 years. Following the initiation of ERT, mean uterine size increased from 8.7 ± 3.8 cm^2 to 10.2 ± 5.6 cm^2, representing a mean percent increase of 134.9% (median observation period of 5.4 years). Similarly, in the CH group, the median age was 25.8 years, and the mean uterine size increased from 9.7 ± 5.6 cm^2 to 14.7 ± 5.2 cm^2 with the initiation of ERT, resulting in a mean percent increase of 220.9% (median observation period of 5.3 years). Concerning treatment response, 62.5% (5 of 8) women in the GH group and 40.0% (2 of 9) women in the CH group exhibited a poor response to ERT.

The correlation between uterine size after ERT and the age of onset of primary disease treatment was examined. In the GH group, a significant positive correlation was observed (Fig. 4A; $p < 0.05$, $R = 0.775$). Conversely, the CH group showed a negative correlation, although not statistically significant ($p = 0.07$, $R = -0.669$), indicating that younger age at primary disease treatment tended to be associated with greater uterine response to ERT. For cases exhibiting poor uterine response ERT, the distribution was found to be independent of the age at which treatment for the primary disease was initiated in the GH group. The CH group observed suboptimal uterine response to ERT in two individuals who underwent primary disease treatment at the ages of 7 and 13, with the former receiving chemotherapy.

The correlation between uterine size after ERT and age at the initiation of ERT was also examined. The GH group did not demonstrate a statistically significant difference; however, a strongly positive correlation was observed (Fig. 4B; $p = 0.12$, $R = 0.636$). This result does not imply that earlier initiation of ERT has a harmful effect on uterine development, but rather suggests that damage to the uterus from radiation exposure at a younger age cannot be improved even with earlier initiation of ERT. On the other hand, the CH group showed no significant, but negative correlation between the timing of ERT initiation and uterine size ($p = 0.39$, $R = -0.351$).

Finally, the correlation between uterine size after ERT and the duration from the start of treatment for the primary disease to the initiation of ERT was investigated. In the GH group, a significant strong negative correlation was observed (Fig. 4C, $p < 0.05$, $R = -0.758$). On the other hand, there was no significant difference between the two variables in the CH group.

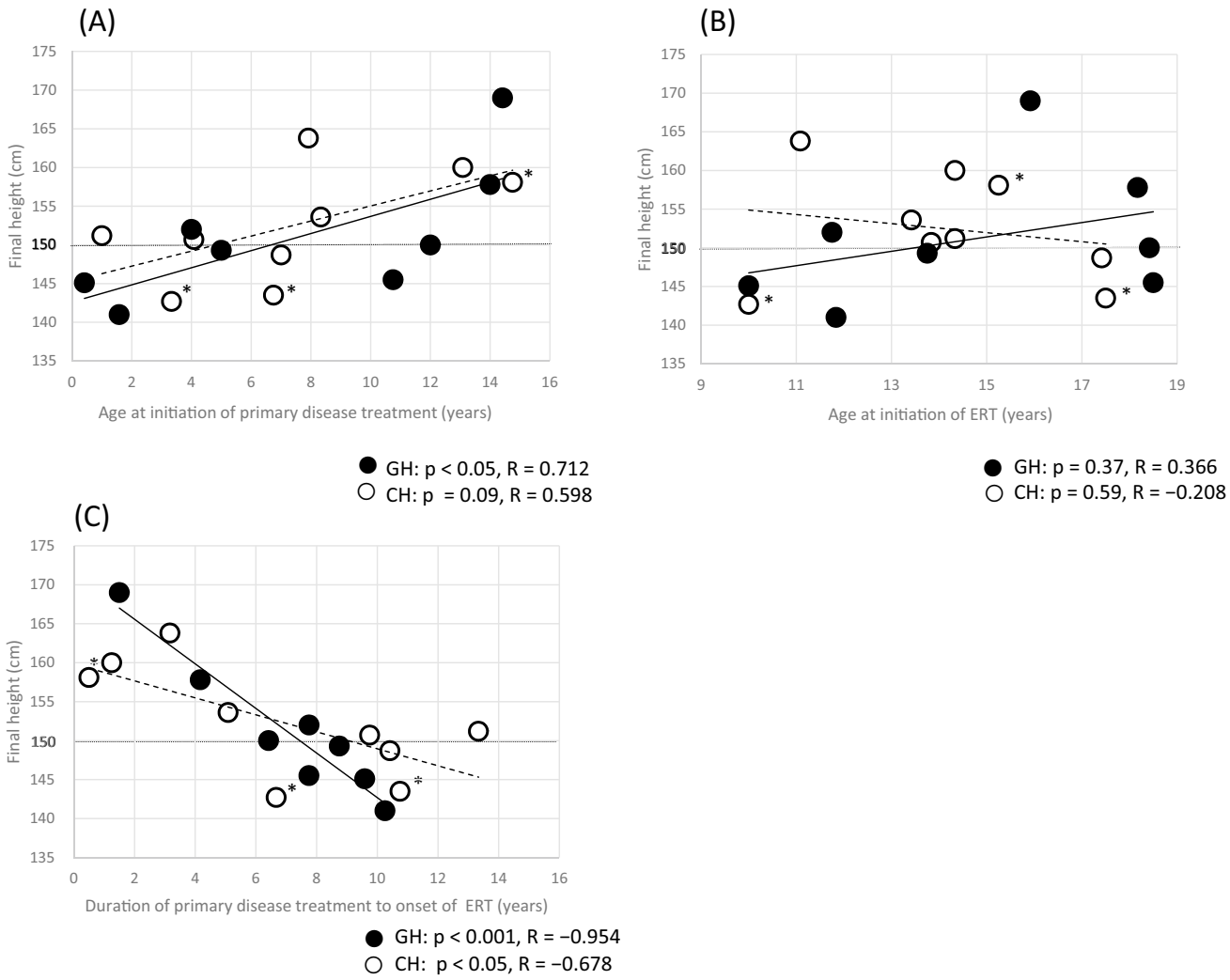

Fig. 2 Impact of age at onset of cancer treatment and estrogen therapy on final height. Correlation analysis between final height and age at onset of cancer treatment (A), age at onset of estrogen replacement therapy (B), and interval between cancer treatment and initiation of estrogen replacement therapy (C). Individuals with gonadal hypogonadism (GH, n = 8) are denoted by closed circles, whereas those with central hypogonadism (CH, n = 9) are represented by open circles. The solid and dotted lines represent the linear regression for GH and CH, respectively. *Cases in the CH group without growth hormone treatment. *ERT* estrogen replacement therapy

Discussion

The significance of managing appearance-related side effects in cancer survivors has recently been recognized [12, 13], with a pressing need to reduce the incidence of short stature in CCS. Our study found that up to 8 out of 17 CCS were below 150 cm in height, highlighting the need for a management policy to prevent short stature. Figure 2B indicates that an earlier age at which ERT is initiated may not contribute to height increase in the GH group. The finding in Fig. 2C is probably not attributed to a delay in commencing ERT but rather to the substantial impact of the younger age at which the treatment of the primary disease commenced on the ultimate height in the GH group. In contrast, the present study suggests that a later age of starting ERT may have a negative effect on height growth in CH patients who received growth hormone therapy. The guidelines recommend growth hormone treatment for CCS with CH to prevent short stature [14–18]. In our study, two-thirds of the CH group received growth hormone treatment, but two out of three cases who did not reach 150 cm did not receive growth hormone treatment in accordance with the results of growth hormone secretion tests. Growth hormone was not administered to the GH group, except for one case of brain tumor, which mostly underwent TBI. However, previous studies report that growth hormone treatment has a beneficial effect on height gain in children with growth disorders following TBI, regardless of the growth hormone secretion status [19,

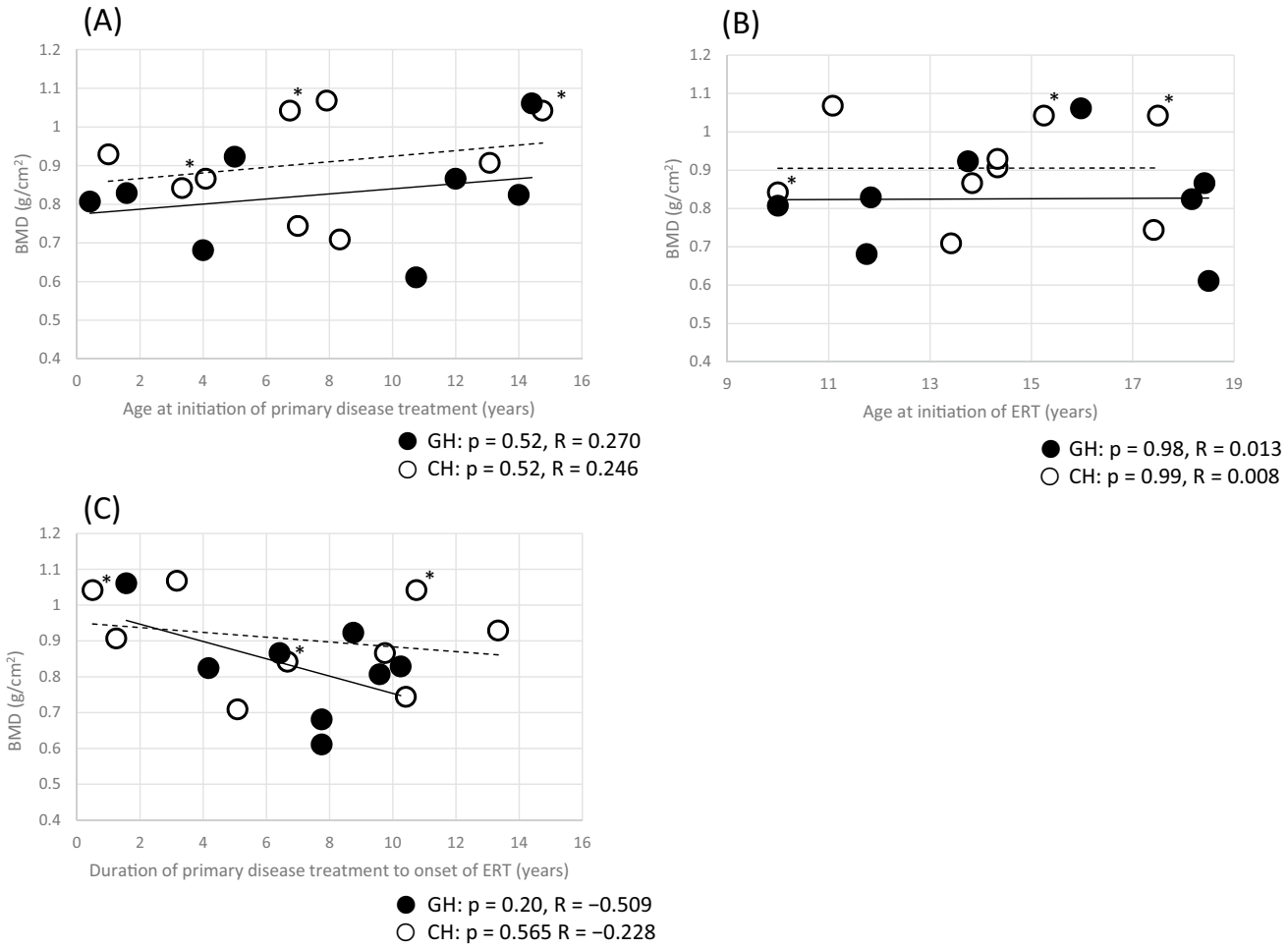

Fig. 3 Impact of age at onset of cancer treatment and estrogen therapy on bone mineral density. Correlation analysis between bone mineral density and age at onset of cancer treatment (A), age at onset of estrogen replacement therapy (B), and interval between cancer treatment and initiation of estrogen replacement therapy (C). Individuals with gonadal hypogonadism (GH, n = 8) are denoted by closed circles, whereas those with central hypogonadism (CH, n = 9) are represented by open circles. The solid and dotted lines represent the linear regression for GH and CH, respectively. *Cases in the CH group without growth hormone treatment. *BMD*, bone mineral density, *ERT* estrogen replacement therapy

20]. In addition to growth hormone and radiation [21, 22], estrogen plays a significant role in bone development [23, 24]. Our analysis revealed that the median age for initiating ERT was delayed at 14 years old, though the median age for treatment of the primary disease was 7 years old. Moreover, one CH case who received growth hormone treatment but did not reach 150 cm had begun ERT after the age of 17. Turner syndrome is a representative disease that causes short stature partly due to decreased growth hormone secretion and estrogen deficiency. Research on Turner syndrome has demonstrated that individuals who received both growth hormone and estrogen had a significantly greater increase in height compared to those who received growth hormone alone [25]. The present study further showed that delayed initiation of ERT was associated with a potential negative impact on final height in CH patients treated with growth hormone. Given these findings, initiating growth hormone treatment at around 4–6 years of age and preferably before 12–13 years of age, and starting low-dose ERT between 11 and 12 years of age, in accordance with the Turner syndrome guidelines [9], may be beneficial for preventing short stature in individuals with hypogonadism-associated CCS, irrespective of the underlying gonadal insufficiency.

Chemotherapy and radiation therapy used in cancer treatments can damage bone tissue and decrease bone mineral density, leading to an increased risk of osteoporosis at a young age. It is widely recognized that ERT plays a critical role in maintaining bone mineral density in hypogonadal patients. Indeed, the present study confirmed that delayed initiation of ERT in CH patients receiving growth hormone therapy may have a negative effect on bone density. Nevertheless, previous studies have shown that the incidence

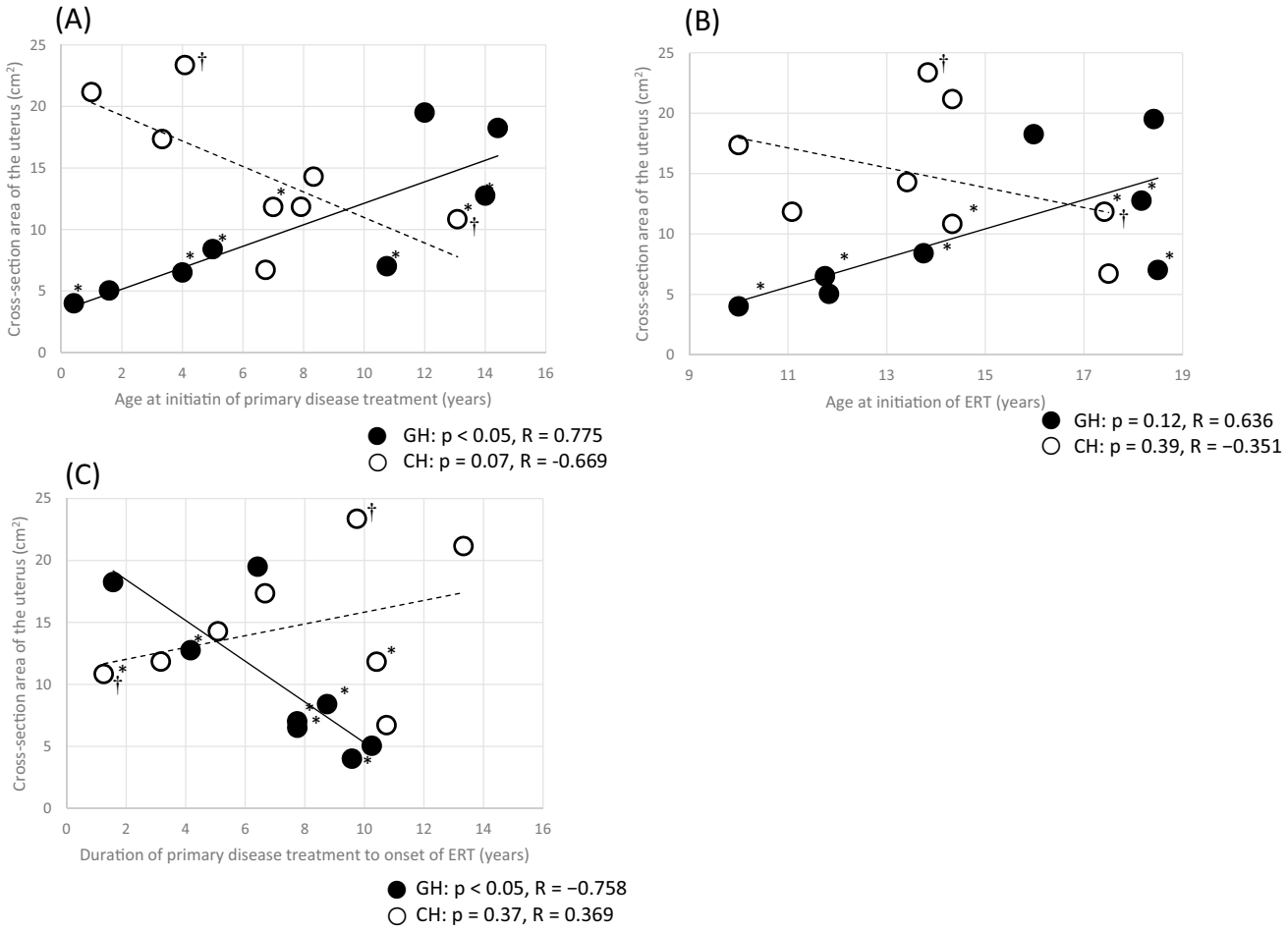

Fig. 4 Impact of age at onset of cancer treatment and estrogen therapy on uterine size. Correlation analysis between uterine area and age at onset of cancer treatment (A), age at onset of estrogen replacement therapy (B), and interval between cancer treatment and initiation of estrogen replacement therapy (C). In the CH group, one lacked data on uterine area after the start of ERT. Individuals with gonadal hypogonadism (GH, n = 8) are denoted by closed circles, whereas those with central hypogonadism (CH, n = 8) are represented by open circles. The solid and dotted lines represent the linear regression for GH and CH, respectively. *; Cases of poor uterine response to estrogen replacement therapy. †; Cases in the CH group without chemotherapy. *ERT* estrogen replacement therapy

of osteoporosis in CCS ranges from approximately 9% to 51% [26]. Our study also found that, among the 17 CCS participants who received ERT, five had bone mass indicative of osteoporosis regardless of the type of hypogonadism, emphasizing the need for multimodal interventions that encompass medications (e.g., bisphosphonates) and lifestyle changes (e.g., regular exercise and a healthy diet) [26]. The consequences of osteoporosis in CCS can be severe, including an increased risk of bone fractures, chronic pain, and reduced mobility, potentially limiting their ability to engage in physical activity and daily life activities [27]. Therefore, CCS should receive appropriate counseling and education on bone health, be made aware of the potential long-term effects of cancer treatment on bone health, and undergo regular bone density assessments to identify early signs of bone loss.

Cancer treatment can adversely affect uterine function in CCS. Both radiation therapy and chemotherapy have been found to negatively impact uterine function, including reductions in uterine volume, endometrial thickness, and uterine blood flow [28, 29]. The Fig. 4B and C indicate that treatment at a younger age for the primary disease may result in irreversible damage to the uterus, rather than suggesting that delayed initiation of ERT after the start of treatment for the primary disease may adversely affect uterine development. The GH group analysis showed that when the uterus was irradiated at a younger age, uterine size did not improve with ERT. This finding is consistent with prior reports [7, 28], where the authors observed no significant improvement in uterine volume, endometrial thickness, and uterine artery blood flow with ERT. In contrast, the CH group analysis indicated that cases receiving chemotherapy before the age

of 6 had significantly larger uterine sizes than those who received chemotherapy between 6 and 10 years of age (pre-pubertal to pubertal period). This result is contrary to that observed in radiation therapy and, to the best of our knowledge, represents the first report in the study of CCS. Ovarian enlargement has been reported to occur after the age of 6 [30], and this phenomenon is believed to prepare the ovary for puberty and the corresponding increase in estrogen production. After the age of 6, the uterus starts to enlarge primarily driven by estrogen secretion from the ovaries [31]. This phase corresponds to a period of heightened cellular division, during which the potential adverse impacts of anticancer drugs on uterine cell may be significant. Our findings suggest that dormant ovaries may exhibit reduced sensitivity to chemotherapy, potentially avoiding a decline in uterine function. At present, fertility-sparing treatments such as ovarian tissue cryopreservation are administered to pre-adolescent cancer patients [32]; however, radiation therapy to the uterus and chemotherapy during the pre-pubertal to pubertal period may severely impair uterine function. As a result, new strategies are required to modify cancer treatment to minimize reproductive system toxicity and preserve the fertility of CCS.

In conclusion, initiating ERT without delay might be crucial in preventing short stature and osteoporosis, particularly in CH patients receiving growth hormone therapy. Moreover, the present sheds light on the limitations of ERT for the management of hypogonadism in CCS and underscored the need for personalized treatment strategies that extend beyond ERT. To minimize the long-term complications associated with hypogonadism in CCS, interventions that consider the type and timing of primary cancer treatment are imperative, in addition to the development of novel therapeutic approaches.

Declarations

Conflict of interest The authors declare no conflicts of interest associated with this manuscript.

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