Ovarian Function and Reproductive Outcomes in the Female Survivors of Childhood and Adolescent Cancer Patients: Review

Hayatta Kalabilen Çocukluk Çağı ve Adolesan Kanser Hastalarında Over Fonksiyonu ve Reprodüktif Sonuçlar

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ABSTRACT In the last 25 years, thanks to new treatment methods, a significant improvement in 5-year survival has been observed in children under 15 year with cancer diseases. This increase has led to the emergence of a new human population: childhood cancer patients who become adult. Unfortunately, children exposed to cytotoxic chemotherapy drugs (alkylating agents and anthracyclines), and radiation undergo many metabolic and endocrine problems. Gonadal (ovarian) failure, failure of reproductive function development and related sequelae have become more noticeable in recent years in children exposed to chemotherapy and/or radiotherapy. Therefore restoration of gonadal function and fertility is of growing importance in these patients. Moreover, same risks also exist in some diseases classified benign (e.g. myelodysplasia , thalassemia, as systemic lupus erythematosus), in which treatment is constituted of chemotherapy and/or radiotherapy and bone marrow transplantation. Due to early and rapid loss of follicles, Turner's syndrome and other disease groups such as galactosemia result in absolute early menopause. As seen preservation of fertility is not only restricted to cancer patients. We aimed by preparing a comprehensive up to date review to clarify readers information. We examined in detail effects of childhood cancer treatment on ovaries , ovarian germ cell dynamics and measurement of ovarian reserve tests.

Key Words: Fertility preservation; antineoplastic protocols; radiotherapy; chemotherapy, adjuvant

ÖZET Son 25 yılda, 15 yaş ve altındaki çocuklarda görülen kanser hastalıklarında yeni tedavi yöntemleri sayesinde 5 yıllık sağkalım sürelerinde belirgin bir iyileşme gözlenmektedir. Bu artış yeni bir populasyonun ortaya çıkışına yol açmıştır: Erişkin yaşa gelen çocukluk çağı kanser hastaları. Bununla birlikte maalesef sitotoksik kemoterapi ilaçları (alkile edici ajanlar ve antrasiklinler) ve radyoterapiye maruz kalan çocuklarda pek çok metabolik ve endokrin problem izlenmektedir. Çocukluk çağında kemoterapi ve/veya radyoterapi uygulanan hastalarda gonadal (over) yetmezlik, üreme fonksiyonlarında yetersizlik gelişmesi ve buna bağlı sekeller son yıllarda daha çok farkedilir hale gelmiştir. Dolayısıyla gonadal fonksiyonların ve fertilitenin korunması bu grup hastalarda giderek önemi artan bir şekilde gündeme gelmektedir. Üstelik benign hastalıklar sınıfında olduğu halde (örn: miyelodisplazi, talasemi, sistemik lupus eritematozus gibi), tedavisi amacıyla kemoterapi ve/veya radyoterapi uygulanması ve kemik iliği nakli gerektiren bazı hastalıklarda da aynı riskler mevcuttur. Turner sendromu ve galaktozemi gibi bir diğer grup hastalıkta ise erken ve hızlı folikül kaybı mutlak erken menopoz ile sonuçlanmaktadır. Görüleceği üzere fertilitenin korunması sadece kanser hastalarına sınırlı değildir. Biz de bu konuda kapsamlı bir derleme hazırlayarak okuyucuları güncel bilgilerle aydınlatmayı hedefledik. Çocukluk çağı kanserlerinde kullanılan tedavilerin over üzerine olan etkilerini, overde germ hücre dinamiğini, over rezervi ölçüm testlerini detaylı olarak irdeledik.

Anahtar Kelimeler: Fertiliteyi koruma; antineoplastik protokoller; radyoterapi; kemoterapi, adjuvan

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Cancer is the second leading cause of death among children between ages 1 to 14, surpassed only by accidents.[1] Nearly one third of the cancers diagnosed in children ages birth to 14 years are leukemias (particularly acute lymphocytic leukemia), followed by cancer of the brain and other nervous system (21%), soft tissue sarcomas (including neuroblastoma [7%] and rhabdomyosarcoma [3%]), renal (Wilms) tumors (5%), and non-Hodgkin lymphoma (4%).[1] Over the past 25 years, the 5-year relative survival rate among children under age 15 years for all cancer sites combined significantly improved from 58% to 81% due to the employment of new and more effective targeted therapies, and chemotherapy and radiotherapy regimens and advancements in diagnostic modalities.[1] Prolonged survival has given rise to a new population, *adult survivors of childhood cancer*. Gonadal (ovarian) failure and other poor reproductive outcomes at long-term are now being recognized as important sequelaes of previous exposure to chemo and/or radiotherapy during childhood.[2,3] Cytotoxic chemotherapy regimens and radiotherapy induce apoptotic death of the follicles in the ovary leading to early exhaustion of follicle stockpile and premature ovarian failure (POF).[4] Unfortunately, end-organ damage is not limited to the ovary. In fertile survivors of childhood cancers who were exposed to pelvic or spinal radiotherapy during childhood, there is an increased risk of early pregnancy loss, preterm birth, and delivery of low- or very-low birth weight infants due to the impact of radiotherapy on the uterus and pelvic structures (Figure 1).[5]

Besides pediatric cancers, patients with certain precancerous and benign illnesses such as myelodysplasia, aplastic anemia, thalassemia, and systemic lupus erythematosus may have to receive high dose chemotherapy with or without hematopoietic stem cell transplantation (HSCT) for the treatment of their primary diseases (Table 1).[2] Moreover, the indications for fertility preservation have also extended to those who are genetically predisposed to POF. Turner syndrome and galactosemia are two striking examples. Both disorders are characterized by accelerated and premature depletion of the oocytes in the ovary, culminating in POF. Therefore, preservation of gonadal function and fertility has become one of the major quality of life issues for pediatric and adult cancer patients. Accordingly, clinical guidelines, encouraging fertility preservation among all young cancer survivors with interest in fertility have been issued by the American Society of Clinical Oncology.[6]

THE IMPACT OF CANCER TREATMENT ON OVARIAN FUNCTION IN THE SURVIVORS OF CHILDHOOD CANCERS

CHEMOTHERAPY

Chemotherapy drugs have different cytotoxicity profiles depending upon their category as shown in the Table 2. Chemotherapeutics of alkylating category such as cyclophosphamide, busulfan and mel-

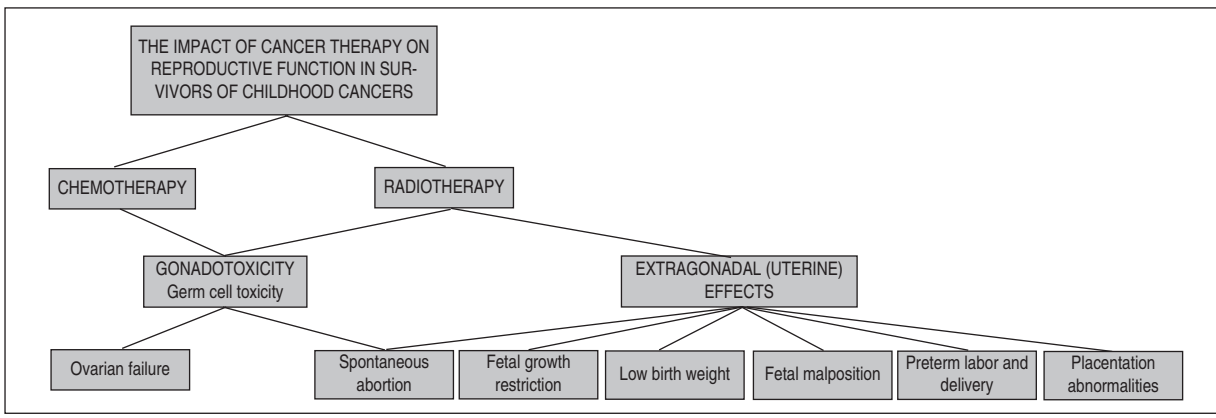

FIGURE 1: The impact of chemotherapy and radiation on the reproductive system in the childhood cancer survivors.

TABLE 1: The diseases requiring counseling for fertility preservation in the children.
The indications extend beyond cancer.

Disease	Indication For Fertility Preservation
Leukemia-Lymphoma	Chemotherapy-HSCT
Myelodysplasia	HSCT
Aplastic anemia	HSCT
Thalassemia major	HSCT
Other hematological diseases	Chemotherapy-HSCT
Autoimmune diseases	Chemotherapy-HSCT
Wegener Disease	Chemotherapy-HSCT
Systemic lupus erythematosis	Chemotherapy
Wilms tumor	Chemotherapy
Osteosarcoma	Chemotherapy
Ewing Sarcoma	Chemotherapy
Tumors of the pelvis and spine	Chemotherapy-Radiotherapy
Retroperitoneal tumors	Chemotherapy-Radiotherapy
Rhabdomyosarcoma	Radiotherapy
Turner Syndrome	Premature ovarian failure
Galactosemia	Premature ovarian failure
Fragile-X syndrome	Premature ovarian failure
Mosaicism	Gonadectomy
Teratoma	Gonadectomy

HSCT: Hematopoietic stem cell transplantation.

phalan have the highest gonadotoxic potential. Unfortunately many of these alkylating drugs are included in the first line therapy of many solid and hematological malignancies commonly diagnosed in children such as Hodgkin lymphoma (HL).[7] A human ovarian xenograft model showed that both oocyte and somatic cells of the follicles (ie, granulosa cells) undergo apoptotic cell death after exposure to cytotoxic chemotherapeutics It should also be noted that cancer drugs with moderate or minimal gonadal toxicity may induce more toxicity in the ovary if they are used for longer period of time; at higher doses; and in patients at advanced age and with poor ovarian reserve.

RADIATION

Direct action of radiation on deoxyribonucleic acid (DNA) is the predominant mechanism of damage for particle radiation such as neutrons and particles. There are also indirect actions that come from the interaction of radiation with other substances in the cell such as water leading to formation of free radicals and DNA damage. Gonadal damage occurs by direct exposure to radiation such as in the case of pelvic or low abdominal or the lumbosacral spinal irradiation.[2] Also scatter radiation may cause significant damage even if the gonads are outside the radiation field. The risk of POF is higher with increasing radiation doses. Single dose appear to be more toxic effects than fractionated dose.[8] Different from chemotherapy, uterine function is also often compromised by radiation. Radiation-induced damage to uterine vascular and muscular structures result in decreased uterine blood flow, reduced uterine volume, decreased endometrial thickness, and loss of distensibility.[2] These changes can potentially lead to adverse pregnancy outcomes such as miscarriages, still births, preterm deliveries in the survivors of childhood cancers.[9] Craniospinal irradiation is another form of radiotherapy commonly used for the treatment of pediatric brain and spinal cord tumors. Even though there is no direct impact of this form of radiotherapy on the ovaries and the uterus, its use may be associated with abnormalities in the reproductive function by causing abnormal pubertal timing and other endocrinopathies.[10]

GERM CELL DYNAMICS IN THE OVARY

Primordial germ cells (PGC) are the embryonic precursors of oocytes. In a newborn ovary approximately one million germ cells are present of which, only three or four thousands will remain at puberty. This is the physiological form of atresia and occurs gradually in years. However, in the pathological form of follicle atresia as occurs after exposure to cytotoxic chemotherapy regimens and radiotherapy follicle loss occurs in an accelerated, premature and massive manner causing early exhaustion of the follicle pool and ovarian failure.

Ovarian reserve is determined by the number of quiescent primordial follicles in the ovary. Since activation of primordial follicles for growth is not under endocrine control of gonadotropins they do not express FSH receptor or produce antimullerian hormone (AMH).[11,12] Therefore there is no hormonal or any other marker of them that guide clinicians to predict their number in the ovary. Any

TABLE 2: Chemotherapy drugs. Chemotherapy agents are classified in the table according to their category and gonadotoxic potential.

Category	Group	Gonadotoxicity
Antimetabolites	**Folic acid:** (Aminopterin, Methotrexate, Pemetrexed, Raltitrexed) **Purine:** (Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Pentostatin, Thioguanine) **Pyrimidine:** (Cytarabine, Decitabine, Fluorouracil/Capecitabine, Floxuridine, Gemcitabine, Enocitabine, Sapacitabine)	• Mild toxicity • Block DNA synthesis • Cell cycle specific (S phase, DNA synthesis) • Possibly more toxic on the growing fraction of the follicle pool at preantral stage and onward due to their higher mitotic rates and metabolic demands
Alkylating Agents	**Nitrogen mustards:** (Chlorambucil, Chlormethine, Cyclophosphamide, Ifosfamide, Melphalan, Bendamustine, Trofosfamide, Uramustine) **Nitrosoureas:** (Carmustine, Fotemustine, Lomustine, Nimustine, Prednimustine, Ranimustine, Semustine, Streptozocin) **Platinum (alkylating-like):** (Carboplatin, Cisplatin, Nedaplatin, Oxaliplatin, Triplatin tetranitrate, Satraplatin) **Alkyl sulfonates:** (Busulfan, Mannosulfan, Treosulfan) **Hydrazines:** (Procarbazine) **Triazenes:** (Dacarbazine, Temozolomide) **Aziridines:** (Carboquone, ThioTEPA, Triaziquone, Triethylenemelamine)	• Alkylating chemotherapeutics are the most gonadotoxic agents. • Targets cells at different stage of cell cycle (not cell cycle specific). They exert selectively more toxicity on resting primordial follicles (cyclophoshamide). • High-dose cyclophosphamide (200 mg/kg) is frequently used as conditioning therapy before bone marrow transplantation (BMT). • Used as the first line therapy for leukemia, lymphoma and other pediatric tumors.
Spindle Poisons Mitotic Inhibitor	**Taxane:** (Docetaxel, Larotaxel, Ortataxel, Paclitaxel, Tesetaxel).	• Less cytotoxic than alkylating agents and platinum group. • Taxanes function as mitotic inhibitor by stabilizing microtubules and as a result, interfering with the normal breakdown of microtubules during cell division. • The vinca alkaloids inhibit assembly of microtubule structures. Disruption of the microtubules arrests mitosis in metaphase. Therefore, the vinca alkaloids affect all rapidly dividing cell types including cancer cells, but also those of intestinal epithelium and bone marrow. • No ovarian toxicity was documented in a small number of women receiving vincristine[27]
	Vinca: (Vinblastine, Vincristine, Vinflunine, Vindesine, Vinorelbine), Ixabepilone	
Cytotoxic Antitumor Antibiotics	**Anthracycline family:** (Aclarubicin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Mitoxantrone, Pixantrone, Valrubicin, Zorubicin) **Streptomyces** (Actinomycin, Bleomycin, Mitomycin, Plicamycin)-Hydroxyurea	• Anthracyclins inhibit DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, thus preventing the replication of rapidly-growing cancer cells. • They also create iron-mediated free oxygen radicals that damage the DNA and cell membranes. • They follow alkylating and platinum compounds in ovarian toxicity. • They inhibit transcription by binding DNA at the transcription initiation complex and preventing elongation by RNA polymerase. • Their gonadal toxicity profiles are similar to anthracyclins.
Topoisomerase Inhibitors	**Camptotheca:** (Camptothecin, Topotecan, Irinotecan, Rubitecan, Belotecan), **Podophyllum:** (Etoposide, Teniposide)	They form a ternary complex with DNA and the topoisomerase II enzyme, preventing re-ligation of the DNA strands. This causes errors in DNA synthesis and promotes apoptosis of the cancer cell. Limited data suggest moderate ovarian toxicity.[28-30]

→ *Continuous.*

TABLE 2: *Continuous.*

Monoclonal Antibodies	**Receptor tyrosine kinase:** (Cetuximab, Panitumumab, Trastuzumab)-CD20 (Ritutumomab) **Other** (Alemtuzumab, Bevacizumab, Edrecolomab, Gemtuzumab)	No data on ovarian toxicity
Tyrosine Kinase Inhibitors	Axitinib, Bosutinib, Cediranib, Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sorafenib, Sunitinib, Vandetanib	No data on ovarian toxicity
Cyclin Dependent Kinase Inhibitors	Alvocidib, Selicicilb	No data on ovarian toxicity
Others	Fusion protein (Afilibercept), Denileukin difititox	No data on ovarian toxicity
Photosensitizers	Aminolevulinic acid, Efaproxiral, Methyl aminolevuiinate, Porfimer sodium, Talaporfin, Temoporfin, Verteporfin	No data on ovarian toxicity
Ungrouped	Retinoids (Alitretinoin, Tretinoin), Anagrelide, Arsenic trioxide, Asparaginase (Pegaspargase), Atrasentan, Bortezomib, Carmofur, Celecoxib, Demecolcine, Elesclomol, Elsamitrucin, Etoglucid, Lonidamine, Lucanthone,Masoprocol, Mitobronitol, Mitoguazone, Mitotane, Oblimersen, Omacetaxine, Sitimagene ceradenovec, Tegafur,Testolactone, Tiazofurine, Tipifarnib, Vorinostat	No data on ovarian toxicity

toxic insult that preferentially targets primordials causes more detrimental effect on ovarian reserve leading to either a decrease in reproductive life span or POF. If the loss of ovarian function develops during or shortly after the completion of cancer therapy, it is termed acute ovarian failure (AOF). For survivors who retain ovarian function after the completion of cancer treatment, a subset will go on to experience menopause before age 40 yr and is classified as having premature menopause (PM).[13]

ACUTE OVARIAN FAILURE

We know that AOF develop at least in a subset of survivors of pediatric and adolescent cancers whereas the precise incidence of AOF is not known, and data concerning its risk factors are limited. The first report of the Childhood Cancer Survivor Study was published in 2006.[13] The study included 3390 female participants from the Childhood Cancer Survivor Study who were greater than 18 years of age showed that 215 patients (6.3%) developed AOF. Survivors with AOF were older at diagnosis and more likely to have been diagnosed with HL or to have received abdominal or pelvic radiotherapy than survivors without AOF. The second report was published in 2009 with longer durations of follow-up and reviewed the frequency of AOF, PM, live birth, stillbirth, spontaneous and therapeutic abortion and birth defects in the participants in the Childhood Cancer Survivor Study.[14] The results has shown that AOF occurred in 6.3% of eligible survivors. Young patients with good ovarian reserve are more likely to retain some residual ovarian function after exposure to cytotoxic cancer therapies or irradiation than older counterparts with diminished ovarian reserve.[7,15,16] The last report of the Childhood Cancer Survivor Study was published in 2013. This study showed that increasing doses of uterine radiation and alkylating agent chemotheraphy were strongly assosiated with infertility. Although survivors had an increased time to pregnancy compared with their siblings (p=0.032), 292 (%64) of 455 participants with self-reported clinical infertility achieved a pregnancy.[17] Sadly, the most devastating effect of

radiation on the ovary occurs in patients who receive a HSCT with high-dose total body irradiation (TBI).[18] Based on the available data it is safe to conclude that most recipients of allogeneic HSCT suffer from infertility owing to gonadal damage from myeloablative conditioning with chemotherapy with and without irradiation.

PREMATURE MENOPAUSE

Premature menopause is another form of gonadal failure characterized by the development of POF in childhood cancer survivors who retained ovarian function after completion of cancer treatment. In this group of patients the loss of ovarian function occurs years after completion of cancer therapy after a window of normal functioning. Using data from the Childhood Cancer Survivor Study, ovarian function was analyzed in 2819 survivors of childhood cancer.[19] The cumulative incidence of nonsurgical PM was higher for survivors than for siblings (8% versus 0.8%). Identified risk factors include attained age, exposure to increasing doses of radiation to the ovaries, increasing alkylating agent score (based on number of alkylating agents and cumulative dose), and a diagnosis of HL. For survivors who were treated with alkylating agents plus abdominopelvic radiation, the cumulative incidence of nonsurgical PM approached 30%.[19] Later 2009 report of the study confirmed the findings showing the same incidence of nonsurgical PM (8% of participants versus 0.8% of siblings (rate ratio= 13.21; 95% CI, 3.26 to 53.51; $p<0.001$).[14] A cohort-study showed that chemotherapy was associated with a 12.3-fold increased risk of PM compared with radiotherapy alone. Alkylating agents, especially procarbazine (HR: 8.1) and cyclophosphamide (HR: 3.5), showed the strongest associations. Ten years after treatment, the actuarial risk of PM was 64% after high cumulative doses (>8.4 g/m^2) and 15% after low doses (<or= 4.2 g/m^2) of procarbazine.[20] Studies show comparable follicle densities in the ovaries in patients undergoing ovarian tissue freezing before and after receiving doxorubicin, bleomycin, vinblastine and darcarbacine (ABVD) regimen.[21]

MARKERS OF OVARIAN RESERVE AND FUNCTION

It is of crucial importance to obtain accurate information on the gonadotoxicity of different cancer treatment regimens to provide the best approaches for fertility preservation. Data on the gonadotoxic potential of cancer drugs are largely collected from 2 important sources; animal studies and clinical trials. Several animal studies, mainly in rodents, showed individual gonadotoxicity of certain cancer drugs such as cyclophosphamide.[22] However, the major drawback of utilizing animals is the differences in ovarian physiology, the mechanisms of action of cancer drugs, or different thresholds of gonadal toxicity between human and the animal tested. The most accurate information of gonadotoxicity on the human ovary can be obtained by real-time quantitative analysis of primordial follicle counts using histomorphological methods in ovarian samples, which necessitates an operation. It cannot be done in clinical settings for ethical and practical reasons. Moreover, as new agents are introduced to adjuvant setting, their long-term impact on the human ovary is extremely difficult to determine from short-term studies.

In clinical studies, the magnitude of the impact of chemotherapy on the human ovary is determined by assessing either menstrual function or the markers of ovarian reserve or both in patients receiving that chemotherapy regimen. It should be emphasized that menstrual status is a crude marker of fertility, as shown previously in patients who were still menstruating despite their critically elevated follicle stimulating hormone (FSH) levels and diminished ovarian reserve.[23] Therefore the presence or return of menstruation at the end of treatment does not necessarily connote normal fertility or reproductive life span. Ovarian reserve markers such as FSH, estradiol, and AMH measurements , as well as antral follicle counts, can give a better estimate of ovarian reserve before and after chemotherapy. Indeed, most data on markers of ovarian reserve and response arise from the clinical context of improving prediction of outcome during assisted reproduction, but has also been translated to the effects of chemotherapy on gonadal function. Unfortunately, in contrast to a preponderance of such studies in

adult cancer patients evaluating the impact of chemotherapy regimens with these markers, there are only a few conducted in pediatric cancer patients. Among those AMH appears to provide a more accurate estimation of ovarian reserve. AMH is produced by the granulosa cells of growing preantral and small antral follicles as a dimeric glycoprotein.[12] A growing body of evidence now suggests that AMH can be used both for assessment of ovarian reserve and prediction of invitrofertilisation (IVF) outcome.[24] A recent study conducted AMH levels lower than 1.4 mg/l, a previously established cut-off value which predicts ongoing pregnancy after assisted reproduction.[25] AMH can be used to identify subgroups of childhood cancer survivors at risk for decreased fertility or POF.

Another study analyzed FSH, LH, estradiol and AMH levels on days 3-5 of a menstrual cycle in thirty three cancer survivors in mean age 19.1+/-4.7 years treated in age 12.0+/-5.6 years for HL (n=16), nephroblastoma (n=7), soft tissue sarcoma (n=4), germinal tumor (n=3), neuroblastoma (n=2), histiocytosis (n=1). Mean AMH levels were lower in all patients that received radiotherapy for the infradiaphragmatic region (17.19+/-14.84 pmol/l) than in controls (29.40+/-13.2 pmol/l; p=0.037). Lowered AMH levels were found in 8 patients treated with chemo- and radiotherapy (4- for HL, 2- for Wilms tumor and 2 - for soft tissue sarcoma).[26]

All these studies underscore the impact of chemotherapy (especially alkylating category) and radiation exposed during childhood on ovarian reserve. Therefore every adult survivor of pediatric cancers and the parents of the children with cancer should be informed about the risks of premature ovarian failure and other reproductive harms caused by chemotherapy and radiation. Examples of such reproductive damage are reduction of uterine blood flow and uterine volume , reduction of endometrial thickness and loss of distensibility. As a result of these changes, in the event of a possible pregnancy in future years, risk of abortion and preterm birth may be increased.

In addition, changes in the timing of puberty, incidence of endocrine system abnormalities may increase in patients who undergo cranial radiotherapy. According to such results, in childhood cancer patients, beside treatment of primary discomfort, detailed information about expected reproductive disfunction that could be encountered should be explained to the family and physicians should be aware of this point.

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