

Potential Endocrine Effects of Anticancer Therapy



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Physician Oncology Education Program
Physicians Caring for Texans



**Cancer Prevention &
Research Institute
of Texas**

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Target Audience

“Potential Endocrine Effects of Anticancer Therapy” is designed for primary care physicians and physician assistants.

Instructions for Completing This Course

Physicians who complete the entire activity, including the knowledge assessment and evaluation, may receive continuing medical education credit. To receive credit, please mail the assessment, the evaluation, and payment in the amount of \$35 to POEP, 401 W. 15th St., Austin, TX 78701, or fax the documents (including credit card information) to (512) 370-1693. If you have any questions, please call (512) 370-1673 or e-mail laura.wells@texmed.org.

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Accreditation

The Texas Medical Association is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Hour Designation

The Texas Medical Association designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

TMA has designated “Potential Endocrine Effects of Anticancer Therapy” for 1.5 hours of education in medical ethics and/or professional responsibility.

Author Disclosures of Commercial Affiliations

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Potential Endocrine Effects of Anticancer Therapy

Learning Objectives

Upon completion of this activity, participants should be able to

1. Outline the implications of cancer survivorship;
2. Restate the potential endocrine effects of anticancer therapy;
3. Review the potential sequelae resulting from hypothalamic dysfunction;
4. Detect hypopituitarism, growth hormone deficiency, hyperprolactinemia, hypothyroidism, or gonadal dysfunction in patients who have undergone anticancer therapy; and
5. Determine the impact of radiation therapy on the skeletal system.

Introduction

Almost every family living in the United States has been touched by cancer in one way or another. More than 10.8 million people, nearly 4 percent of the American population, have survived a diagnosis of cancer. As of early 2005, approximately 417,000 people living in Texas survived a cancer diagnosis within 10 years.¹ This number is expected to grow thanks to heightened awareness of cancer prevention and improved detection and treatment.

Although most cancer survivors lead active and productive lives, some may experience a series of problems. Exposure to cancer and its treatments may leave unwanted effects that could either linger or exacerbate over the years. In addition to undesired health effects, some survivors may experience problems keeping medical insurance coverage, finding gainful employment, or maintaining optimal interpersonal relationships.

Early treatment regimens were designed to cure cancer at all costs, but over the years treatment has evolved to encompass improving survivors' quality of life and decreasing the potential of comorbidities. Furthermore, follow-up care for cancer survivors also has evolved from a focus on prevention and detection of relapses to addressing a large spectrum of long-term effects of cancer and cancer treatments. As their numbers and their long-term health care needs increase, survivors of cancer

are expected to take up an increasing portion of national public health care resources. To better address the needs of these survivors, the Institute of Medicine and the National Research Council recently issued recommendations for their long-term follow-up care and for research in that area.²

Long-term health effects that persist throughout the adult lives of childhood cancer patients have been well studied and published. However, the published literature about the unwanted effects of therapy on survivors of adult cancers remains limited. A large percentage of the existing research studies were published decades ago, when the focus of cancer management was on aggressively securing survival. The study of late effects is ongoing as older anticancer therapy regimens are phased out in favor of new ones with less potential for comorbidities.

At The University of Texas M.D. Anderson Cancer Center, the Life After Cancer Care (LACC) program was established to systematically analyze the health profiles of various groups of cancer survivors and to better address appropriate strategies for their ongoing health care by gathering information on the long-term effects of cancer therapies on cancer survivors³⁻¹¹ and their quality of life.^{5, 12, 13}

Among the most serious and understudied long-term health effects that survivors of cancer, including those living in the state of Texas, experience long after their diagnosis is damage by cancer therapy to the endocrine system

Physician Oncology Education Program

Making Every Physician's Office a Cancer Detection and Prevention Center

History

The Texas Medical Association formed the Physician Oncology Education Program (POEP) in 1987 to carry out the recommendations of the Texas Cancer Plan regarding physician education. The POEP is funded by the Cancer Prevention and Resource Institute of Texas and is directed by a steering committee of experts interested in and knowledgeable about all facets of cancer prevention, detection, and control.

Focus

Educating primary care physicians about state-of-the-art and science in cancer prevention, screening, early detection, and control, including the physician role in influencing patient behavior.

Available Resources

Educational Materials

The POEP has developed a number of cancer education resources and clinical tools for the practicing physician. These materials have been designed by physicians and cancer experts to enhance the primary care physician's ability to reduce cancer morbidity and mortality in Texas.

Speakers' Bureau

One of the strongest projects of our nonprofit organization is our Speakers' Bureau. Volunteer physicians and other cancer experts travel around the state to give requested lectures on more than 100 cancer-related topics, including pain management, the human papillomavirus vaccine, and new therapies and treatment options. The POEP reimburses the speaker for travel expenses. There is no fee to the requesting organization.

For a full listing of materials or Speakers' Bureau topics, please visit www.poep.org.

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(including the pituitary and thyroid gland), the reproductive system, and the skeletal system. Susceptibility to the toxic effects of therapy differs among the endocrine glands. For instance, the testes are more sensitive to the toxic effects of chemotherapy and radiation because of the high spermatogenic rate. Cranial irradiation can leave a host of endocrinologic problems including pituitary deficiencies. Some treatment regimens require manipulation of the endocrine system, for example, the hypothalamus-pituitary-gonadal axis. Many cytotoxic drugs do not discriminate between normal tissue and tumor cells. Other problems such as osteoporosis and metabolic disorders may be caused both directly and indirectly by damage to the endocrine glands.

The aim of this review is to discuss potential effects of cancer therapy on the pituitary and thyroid gland, gonads, and skeletal system.

The Pituitary Gland

Damage to the pituitary gland often has been associated with irradiation, surgery, and, in very rare instances, chemotherapy. The preferred methods to treat malignancies affecting the hypothalamic-pituitary axis are surgery and radiotherapy.

The hypothalamus is more sensitive than the pituitary to the effects of radiation, and hypothalamic dysfunction stemming from irradiation of the cranial region can be delayed and linger for many years. Incidences of endocrine dysfunction resulting from damage to the hypothalamus-pituitary axis may range from 8 percent to as high as 100 percent.^{14,15}

Potential sequelae resulting from hypothalamic dysfunction include hypopituitarism, growth hormone (GH) deficiency, hyperprolactinemia, hypothyroidism, and gonadal dysfunction. The review by Toogood¹⁶ suggested that the number of pituitary hormone deficiencies increases with the length of time since the completion of radiotherapy, and several studies have highlighted the association between the total radiation dose and the development of pituitary hormone deficiencies.^{15, 17, 18} The

pathophysiology of radiation-induced hypothalamus-pituitary damage remains understudied, although Chieng et al suggested that the harmful effects of radiation to the hypothalamus resulted in direct neuronal damage rather than vascular injury.

Hypopituitarism

Other than pituitary adenomas and brain tumors, craniospinal irradiation has been the most frequently observed cause of hypopituitarism in survivors of cancer, especially for adult survivors. The 10-year overall risk for secondary hypopituitarism from radiotherapy was determined to range between 40 and 80 percent.^{20, 21}

There are published reports of pituitary deficiencies caused by stereotactic radiosurgery^{22, 23} and exposure to interferon.^{24, 25} Littlely et al reported that the likelihood of hypopituitarism was dependent on the total radiation dose.¹⁷ This finding was confirmed by Bhandare et al, that the incidence of deficiency increased with the dose.²⁶ Studies have not been able to agree whether radiation-induced hypopituitarism results from damage to the hypothalamus or to the pituitary gland.^{26, 27}

Agha et al and Bhandare et al could

not determine an association between chemoradiotherapy and hypothalamus-pituitary deficiency^{18, 26} or that sex, age, or ethnicity was a risk factor of the development of radiation-induced hypopituitarism. The incidence of pituitary deficiency was determined to be progressive since the completion of radiotherapy.²⁰

Growth Hormone Deficiency

Growth hormone is the most sensitive of the pituitary hormones to the effects of radiation and is usually the first to exhibit symptoms of damage. Growth hormone deficiency is the most frequently reported endocrine dysfunction in long-term survivors of childhood cancer who were treated with cranial irradiation. The influence of radiation on GH deficiency, including physical stature, depends on the dose²⁸ and age,²⁹ with younger age a risk factor for limited physical growth. Symptoms other than the effect on physical stature may not surface for at least 10 years after treatment. A French study demonstrated that after cranial irradiation, somatotrophic function is the first condition affected, with 90 percent of the patients becoming GH deficient within 10 years after treatment,³⁰ while Darzy et al suggested that after high radiation doses (between 30 and 50 Gy) the

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frequency of GH deficiency in patients can reach high as 100 percent.¹⁵ The addition of chemotherapy appeared to exacerbate the deleterious effects of radiotherapy on GH function.³¹

Adults with GH deficiencies resulting from irradiation for childhood cancer exhibit increased adipose mass, reduced bone mineral density, decreased lean mass, abnormal lipid profile including insulin resistance, and decreased quality of life.

There has been little consensus on the direct role of GH deficiency on bone loss. Much of GH's effect on skeletal cells is regulated through insulin growth factor-I (IGF-I), which plays an important anabolic role in stimulating bone formation and maintaining bone mass.³² The review by Doga et al reported that the fracture rate in GH-deficient adults was twice that of the non-GH-deficient population,³³ and Colao et al³⁴ demonstrated that the degree of bone loss in patients corresponded with the severity of GH deficiency. Reports have suggested that the increased fracture risk in GH-deficient adults may be attributed to GH deficiency alone rather than to other pituitary hormone deficiencies or their replacement therapy.^{35, 36} Patients whose GH levels became deficient during adulthood displayed lower bone mineral density than did normal subjects, and their degree of bone loss was directly associated with circulating IGF-I levels.³⁷

Hyperprolactinemia

Cranial irradiation can result in hyperprolactinemia, in which damage to the hypothalamus renders it unable to inhibit prolactin secretion from the anterior pituitary gland due to the reduced release of dopamine. Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamus-pituitary axis and is evident in both sexes and at all ages, although it is seen most frequently in female patients after high-dose radiation and is often overlooked during clinical screenings.

Untreated hyperprolactinemia can lead to menstruation abnormalities (including amenorrhea) in women, erectile dysfunction and hypogonadism in men, and insulin resistance in both sexes. Central hypogonadism secondary to hyperprolactinemia has been implicated in the development of osteoporosis in both men and women.³⁸ In addition, Vartej et al³⁹ concluded that the relative risk for developing osteoporosis in premenopausal women with prolactinomia was 4.5, demonstrating that hyperprolactinemia in premenopausal women is indeed a major risk factor for osteoporosis. Another report by Colao et al⁴⁰ demonstrated osteopenia and osteoporosis in adolescents with prolactinomia-induced hyperprolactinemia.



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Central Hypothyroidism

Central hypothyroidism results from damage to the hypothalamus-pituitary-thyroid axis, often from irradiation, where deficiencies of the thyrotropin-releasing and thyroid-stimulating hormones may occur. Central hypothyroidism is frequently a result of radiation greater than 30 Gy to the hypothalamic-pituitary axis,⁴¹ especially in children.⁴² The incidence of central hypothyroidism appears to correspond with the radiation field, dose, type of tumor, and interval of time since treatment.⁴¹ The actual prevalence has not been determined because it is often overlooked during standard laboratory screenings. It has been observed in 20 to 50 percent of patients who received radiotherapy for nasopharyngeal or paranasal sinus malignancies and in 6 to 65 percent of those irradiated for brain malignancies.^{43,44} Published literature does not concur on how chemotherapy can exacerbate the damaging effects of radiation on the thyroid axis.

Gonadotropin Deficiency

Gonadotropin deficiency can result from radiation to the hypothalamus-pituitary-gonadal axis where the luteinizing hormones (LH) and follicle-stimulating hormones (FSH) are damaged. The deficiency is more frequently observed after a total radiation dose greater than 40-50 Gy,^{15, 18, 28} with the severity corresponding to the cumulative dose. It is the second most common radiation-induced anterior pituitary hormone deficiency in both pediatric and adult cancer survivors. Secondary hypogonadism from gonadotropin deficiency can result from untreated hyperprolactinemia in which the ability of the pituitary gland to secrete gonadotropins and respond to gonadotropin-releasing hormone is suppressed.⁴⁵ Female patients with gonadotropin deficiency may experience precocious or early puberty, amenorrhea, or hypogonadotropic hypogonadism, and male patients experience lack of libido, impotence, azoospermia, or infertility.

In addition to surgery and radiotherapy, hormone therapies used in cancer treatment protocols may induce gonadotropin dysfunction, include those using

selective estrogen-receptor modulators (SERMs), aromatase inhibitors, androgen deprivation therapy (ADT), megestrol acetate, and glucocorticoids. Hormone therapies are necessary to treat such hormone-sensitive malignancies as breast, ovarian, endometrial, and prostate cancers by reducing the level of estrogen or testosterone in the body and to inhibit the hormone receptors from giving malignant cells the hormones they need to grow. In most instances, the goal of hormone therapy is to actually induce gonadotropin deficiency, effecting estrogen deficiency in women and testosterone deficiency in men in order to control the malignancy. While infertility is an anticipated effect of hormone therapy, another major undesired lingering effect is osteoporosis. Estrogen exerts a protective effect on bone by stimulating new bone cells and inhibiting bone resorption; in hypogonadal patients, decreased circulating estrogen or testosterone levels result in accelerated bone loss by activating the osteoclasts and increasing the death rates of osteoblasts.⁴⁶

Some ADTs include gonadotropin-releasing hormone analogues which, after longtime exposure, can suppress the pituitary gland's secretion of FSH and LH, resulting in decreased secretion of estrogen. In addition to its role in cancer treatment regimens, synthetically induced estrogen deficiency can lead to decreased bone mineral density and ultimately osteoporosis.

The rate of bone loss from ADT exposure can be as much as 10-fold higher than that due to normal aging or female menopause.⁴⁷ Kiratli et al determined a correlation between decreased hip bone mineral density and increasing years of ADT exposure, and the increase was more dramatic in surgically castrated patients than those who receive ADT.⁴⁸

The mechanism of bone loss from ADT use in male cancer survivors has not been fully determined. Theories include the absence of circulating testosterone, which limits the proliferation of osteoblasts in bone tissue by bonding to androgen receptors, and the reduced ability to convert from testosterone to estrogen, which is needed for the maintenance of bone mass.⁴⁹

Aromatase inhibitors, often used in hormone-receptive breast and ovarian cancer regimens, can cause loss of bone mineral density by interfering with the conversion of adrenal androgens to estrogen, which eventually results in reduced circulating and tissue levels of estrogen.⁵⁰ The overall effects of steroidal vs. nonsteroidal aromatase inhibitors are controversial.⁵¹ McCloskey et al found no statistically significant differences among the effects of three aromatase inhibitors (letrozole, exemestane, and anastrozole) on bone loss in postmenopausal women.⁵² Vitamin D deficiency resulting from the use of aromatase inhibitors has been studied as perhaps the most important factor in bone loss in patients taking aromatase inhibitors.⁵³

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Tamoxifen, a SERM, can both cause and prevent bone loss depending on the woman's menopausal status. It works as a bone antagonist in premenopausal women with elevated estrogen levels and as a protective bone agonist in postmenopausal women with hypoestrogenemia. The actual effect of tamoxifen on bone is rather complicated because most current treatment regimens for breast cancer call for adjuvant therapy with aromatase inhibitors after several years of tamoxifen therapy, and trying to determine the role of each agent on bone has challenged researchers.

Prolonged exposure to glucocorticoids, often used in the treatment of hematopoietic-based malignancies, can inhibit LH and FSH secretion, causing suppressed gonadotropin levels, which in turn can exert a direct negative effect on bone. The mechanisms underlying the negative effects of glucocorticoids on bone's microarchitecture include the direct inhibitory effects on osteoblast function, reduction in the production of estrogen and testosterone along with the inhibition of anabolic action of sex steroids, and enhanced effects of parathyroid hormone.⁵⁴ Osteoporosis develops in approximately half of patients on long-term glucocorticoid treatment,⁵⁵ and the risk of fractures

can increase to 100 percent with exposure to oral corticosteroids.⁵⁴

Megestrol acetate, a progestational agent often used in the treatment of breast, endometrial, and prostate cancers, has been associated with osteoporosis and fractures through its glucocorticoid-like activity. Wermers et al demonstrated that high-dose megestrol eroded bone density and contributed to the development of fractures in a cohort of patients.⁵⁶

Adrenocorticotropic Hormone Deficiency

While adrenocorticotropic hormone (ACTH) deficiency is among the least-common observed pituitary hormone disorders, its consequences can be the most serious. Often overlooked during endocrine function testing in survivors, untreated ACTH deficiency may result in reproductive failure and fatal adrenal dysfunction. Symptoms of ACTH deficiency are overlooked in patients with other effects caused by anticancer therapy, especially hypopituitarism and panhypopituitarism, and they may not appear for several years after completion of treatment.

ACTH deficiency may be induced by intensive high-dose cranial irradiation,

but in extraordinary cases. Darzy et al reported that around 3 percent of patients receiving radiation less than 50 Gy developed ACTH deficiency and that it has not been observed in patients who underwent total-body irradiation.¹⁵

ACTH deficiency also can be caused by prolonged glucocorticoid therapy. Suppression of the hypothalamus-pituitary axis by longtime exposure to glucocorticoids can result in atrophied adrenal glands. Secondary hypoadrenalism was associated with prolonged use of busulfan in the 1960s, but no recent published studies confirm the association.

The Thyroid Gland

Hypothyroidism

The direct effects of cancer therapy on thyroid function are still under investigation. While the association between radiotherapy and thyroid function has been recognized, the effects of adjuvant chemotherapy in addition to radiotherapy remain inconclusive. Some studies have suggested that the addition of chemotherapy to radiation protocols involving the thyroid gland is associated with higher incidence of thyroid dysfunction,⁵⁷ while others found no such association.⁵⁸⁻⁶⁰

The first link between interferon- α and hypothyroidism was reported in 1985 in a cohort of breast cancer patients⁶¹ and confirmed thereafter in other studies.^{62, 63} Cytokine-induced hypothyroidism has been attributed to autoimmune thyroiditis.⁶⁴ Other therapeutic drugs used in various cancer treatment protocols — including tyrosine kinase inhibitors, retinoids including bexarotene and retinoic acid,⁶⁵ combined antineoplastic regimens,⁶⁶ exemestane,⁶⁷ and (in very rare instances) growth hormone treatment⁴³ — have been associated with either primary or central hypothyroidism.

Incidences of thyroid dysfunction resulting from exposure to sunitinib may range from 27 to 53 percent.^{68, 69} In one study, 36 percent of patients taking sunitinib for gastrointestinal stromal tumors developed persistent primary hypothyroidism after an average of 50 weeks of treatment.⁷⁰ This latter study and the one by Dora

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et al suggested that the risk of hypothyroidism increased with the duration of therapy.^{70,71} The report by Dora et al suggested that the follicular cell apoptosis following exposure to sunitinib may result in destructive thyroiditis. However, the study by Wolter et al could not discern an association between the daily dose of sunitinib and the development of thyroid dysfunction.⁶⁸

The actual molecular mechanisms of sunitinib-induced hypothyroidism have not been determined, but the morbidity has been attributed to the drug's effect on the thyroid endothelium.⁶⁹ Several studies have not been able to associate hypothyroidism with imatinib, another tyrosine kinase inhibitor in nonthyroidectomized patients.⁷⁰⁻⁷² A clinical study conducted in the Netherlands was the first to report imatinib-induced hypothyroidism in postthyroidectomy patients taking levothyroxine;⁷³ de Groot et al⁷⁴ was able to reconfirm in a later study that imatinib exposure induced hypothyroidism in a female patient taking levothyroxine after thyroidectomy. It was suggested that the stimulation of thyroxine (T4) and triiodothyronine (T3) clearance was a possible mechanism for imatinib-induced hypothyroidism.⁷³ Sorafenib has also been implicated in hypothyroidism in patients,⁷⁵ although further studies are needed to confirm the association.

Primary hypothyroidism as a result of cancer therapy is more frequently seen in patients following cranial and neck irradiation compared with central (or secondary) hypothyroidism; perhaps it is more easily detected during routine laboratory screenings.

Primary hypothyroidism affects between 20 and 30 percent of patients treated with cervical neck node radiotherapy at therapeutic doses between 30 and 70 Gy.⁷⁶ The likelihood of hypothyroidism depends on the treatment received, and it is more likely to occur after total laryngectomy with adjuvant radiotherapy as opposed to either radiotherapy combined with neck dissection or radiotherapy alone. It was suggested that the incidence of hypothyroidism corresponds with higher doses of irradiation on the thyroid gland or whenever it is included with the radiation field used to treat the

primary malignancy. In addition, probability of developing thyroid deficiency likely continues to increase with each year since follow-up.⁷⁷ Sex and thyroid volume have been determined by Alterio et al⁷⁸ to be factors in hypothyroidism in patients treated with radiotherapy for head and neck cancer.

The Gonadal Glands

The two primary roles of the gonads, the production of sex hormones (including testosterone and estradiol) and the regulation of fertility, are both regulated by the hypothalamic-pituitary-gonadal axis. Damage to the hypothalamus-pituitary-gonadal axis by anticancer therapies has been discussed already in this review. Gonadal dysfunction is perhaps one of the most extensively studied long-term effects of cancer therapy and is recognized as the most common adverse effect of chemotherapy in survivors of childhood cancers. Gonadal function can become permanently impaired in patients who underwent regimens containing intensive chemotherapy or total-body irradiation or who received direct high-dose radiation exposure. Combined radiation and chemotherapy regimens can be particularly harmful to the gonads.

The effects of cancer treatment on gonadal function vary by sex. In women, sensitivity to chemotherapeutic or radiation-induced damage is dependent on the patient's age;

younger ovaries are more resilient against damage, and their function can be normalized after completion of standard-dose treatment. However, infertility may occur during severe impairment of oocyte or granulosa cells, and temporary cessation of ovulation and menstruation stems from damage to the maturing follicles. Permanent infertility occurs when the number of surviving primordial follicles falls below the minimum needed to maintain hormone production. Exposure of granulosa cells to cytotoxic drugs may result in the death of oocytes and estrogen deficiency. There is no mechanism in place to replace oocytes damaged or killed by chemotherapy.

In male patients, the testes are particularly sensitive to the effects of chemotherapy and radiation owing to their spermatogenic function. Testosterone and male pubertal development are not usually affected, and if enough germ cells remain after anticancer therapy, the recovery of spermatogenesis is likely. Leydig cell failure is extremely rare and often considered subclinical.

Chemotherapy-induced gonadal toxicity in both men and women patients is highly dose dependent and primarily associated with alkylating agents, including procarbazine, cisplatin, cyclophosphamide, chlorambucil, and melphalan.⁷⁹⁻⁸² Alkylating agents alter the DNA of cancer cells by cross-linking via alkylating action, which prevents them from dividing. It has

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been challenging for researchers to determine the toxicity of individual drugs on the gonads because these drugs are almost always administered in multiagent protocols.

Cyclophosphamide has been identified as the drug in multiagent treatment regimens most responsible for inducing chemotherapy-related amenorrhea.⁸³ The higher the cumulative dose of cyclophosphamide, the higher the possibility of amenorrhea.⁸⁴ Age is a risk factor, with older women more likely to experience amenorrhea.

The prevalence of chemotherapy-induced amenorrhea has ranged from 21 to 71 percent in women younger than 40 years and from 40 to 100 percent in women older than 40 years of age.^{85,86} The use of busulfan in many bone transplantation regimens for hematopoietic malignancies has proven to be highly gonadotoxic, and several reports have indicated that up to 100 percent of girls and young women who received busulfan experienced irreversible ovarian failure.⁸⁷⁻⁸⁹

It has been suggested that the addition of tamoxifen to adjuvant chemotherapy regimens may increase the likelihood of amenorrhea.⁸² Furthermore, Walshe et al,⁸² Han et al,⁹⁰ and Tham et al⁸⁶ demonstrated that the addition of taxanes resulted in higher rates of amenorrhea, especially in women older than

40 years of age. Primary ovarian insufficiency also has been observed after prolonged use of imatinib, a tyrosine kinase inhibitor, but further studies will be needed to confirm the association.⁹¹

Studies have reported azoospermia with elevated levels of FSH in a majority of patients who were treated with alkylating agents or procarbazine.^{28, 92, 93} Similar to its effect observed in women, cyclophosphamide also has been implicated with the highest risk of infertility in men at any age.⁹⁴ Use of the MOPP regimen (mustargen, vincristine, procarbazine, and prednisone), an older protocol once favored for treating Hodgkin's lymphoma, has been associated with a high degree of permanent sterility in patients, especially in men.⁹⁵ Rautonen et al⁹⁶ and Bokemeyer et al⁹³ suspected that vincristine-based regimens were linked with the higher risk of azoospermia in young men. Age at chemotherapy was determined not to correlate with the sperm count; therefore being of prepubertal age did not protect the gonads from the late effects of chemotherapy.⁹⁷

The gonads are sensitive to radiation, with the extent of damage dependent on the field of treatment, total dose, and schedule. Ovarian function can be compromised if the ovaries fall within the fields of pelvic, abdominal, and spinal radiation regimens. Ovarian

Useful Internet Resources

The following links provide physicians with current, scientifically-sound so that they may educate themselves and appropriately refer their patients to reliable sources for information.

Physician Oncology Education Program

www.poep.org

M.D. Anderson Cancer Center — Life After Cancer Care

www.mdanderson.org/Departments/LACC/

Cancer Prevention and Research Institute of Texas

<http://www.cprit.state.tx.us/>

National Cancer Institute Cancer Survivorship Research

<http://cancercontrol.cancer.gov/ocs/office-survivorship.html>

Institute of Medicine — From Cancer Patient to Cancer Survivor: Lost in Transition

<http://www.iom.edu/?id=31512>

American Society of Clinical Oncologists

<http://www.asco.org/>

American Cancer Society

www.cancer.org

Lance Armstrong Foundation

www.laf.org

National Coalition for Cancer Survivorship

<http://www.canceradvocacy.org/>

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93. Bokemeyer C, Berger CC, Kuczyk MA, Schmoll HJ. Evaluation of long-term toxicity after chemotherapy for testicular cancer. *J Clin Oncol*, 1996. 14(11): p. 2923-32.
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failure is dependent on not only the dose but also the age of the patient: the older the patient, the lower the dose needed to induce permanent ovarian failure, and as indicated previously, the remaining population of primordial oocytes falls with age. While radiation doses of 600 cGy may induce permanent ovarian failure in women older than 40 years of age, doses greater than 2,000 cGy may result in irreversible ovarian failure in the majority of females treated during childhood.⁹⁸ The review by Sklar⁹⁹ suggested that ovarian dysfunction can occur with lower radiation doses if given in association with alkylating agents.

In male patients, the germinal epithelium is one of the tissues most sensitive to the effects of radiation. Compromised spermatogenesis can occur with very low doses, and infertility with fractionated doses higher than 2 Gy.¹⁰⁰ While there is no established threshold above which permanent azoospermia is unavoidable, a review by Howell and Shalet⁹² reported that azoospermia may be inevitable after doses higher than 6 Gy. The effect of radiation on Leydig cell function has been challenging to determine because most radiation treatments are given concurrently with chemotherapy. The review by Izard speculated that Leydig cell failure in adolescents and young men can result from testicular doses greater than 3,300 cGy.¹⁰¹

In addition to its damaging effects on gonadal function, radiation has resulted in reduced bone mineral density and increased susceptibility for fracture in patients made hypogonadic by other cancer treatments. Iyer et al reported that the effect of pelvic radiation on bone may not be a direct consequence of the radiation itself but rather an indirect effect of radiation-induced hypogonadism.¹⁰²

The Skeletal System

The first association of radiation and bone damage was reported as early as 1926.¹⁰³ The study by Williams and Davies¹⁰⁴ suggested that radiation damages bone in children by disrupting the chondrogenesis and reabsorption of the calcified cartilage in immature skeletons and in adults by altering the

osteoblasts to inhibit matrix formation. Studies suggest that radiation to the abdominal area for breast cancer and other malignancies, including Hodgkin's lymphoma, can result in radiation osteitis involving the ribs, clavicles, and scapulae.¹⁰⁵ Pelvic irradiation for ovarian/cervical and prostate cancers has been reported¹⁰⁶ to be a predisposing factor for sacral and femoral neck fractures. Libshitz and Edeiken reported several cases of slipped upper femoral epiphysis in a cohort of pediatric cancer patients who were treated with pelvic radiation.¹⁰⁷

Several chemotherapeutic agents such as platinum-based compounds, cyclophosphamide, doxorubicin, cyclosporine, interferon- α , and valproic acid have been reported to injure bone tissue. Cis-platinum has hypomagnesemic effects that can hinder bone growth by inhibiting osteoblast activity. Doxorubicin inhibits the proliferation and differentiation of osteoblasts and indirectly reduces bone formation by altering the parathyroid hormone's interaction with the osteoblast receptor.¹⁰⁸ In addition to its role in promoting hypogonadism, cyclophosphamide slows bone formation and resorption by suppressing the cell division of preosteoblasts and osteoblasts.⁴⁷ Cyclosporine appears to stimulate osteoclasts, suppress osteoblasts, and interfere with the mineral apposition and bone formation rates.¹⁰⁹ The actual effect of cyclosporine on bone has

been difficult for researchers to determine because it has been administered routinely in conjunction with other agents such as corticosteroids, which are also known to cause bone loss.

The exact mechanism of the effect of interferon- α on bone has not been determined. The review by Pfeilschifter and Diel¹¹⁰ suggested that it transformed the cellular functions of osteoblasts and osteoclasts, but Beresford et al¹¹¹ found that it suppressed the proliferation of bone cells but did not appear to enhance differentiation. The effect of valproate on bone has not been identified; however, published literature demonstrates that the agent has been associated with reversible Fanconi syndrome in which it may induce renal tubular dysfunction by increased urinary loss of calcium and phosphate, ultimately resulting in decreased mineral substrates necessary for bone formation.¹¹² Hypophosphatemia resulting from anticancer therapies can also be attributed to vitamin D deficiency, exposure to ifosfamide, and tyrosine kinase inhibitors. The harmful effect of phosphate deficiency on bone has been documented.¹¹³

Hyperparathyroidism as an indirect effect of cancer therapy may have a harmful effect on bone mineral density. Prolonged glucocorticoid exposure, radiotherapy, and organ transplantation may lead to an overactive parathyroid hormone. Hyperparathyroidism quickly

98. Wallace WH, Shalet SM, Hendry JH, Morris-Jones PH, Gattamaneni HR. Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. *Br J Radiol*, 1989. 62(743): p. 995-8.

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113. Grey A, O'Sullivan S, Reid IR, Browett P. Imatinib mesylate, increased bone formation, and secondary hyperparathyroidism. *N Engl J Med*, 2006. 355(23): p. 2494-5.

matures the osteoclasts through the activation of osteoblasts. Osteoclasts release hydrochloric acid, which can erode bone mineral, resulting in osteoporosis.¹¹⁴

Summary

The endocrine system is highly sensitive to the effects of anticancer therapies. While several undesired effects such as hypogonadism may occur during treatment or immediately afterwards, other effects, including osteoporosis and hypopituitarism, may not develop for years afterwards. Some of the more uncommon endocrine dysfunctions such as central hypothyroidism, hyperprolactinemia, and ACTH deficiency are often overlooked or misdiagnosed during follow-up visits. It is important for physicians who treat cancer survivors to be cognizant of various potential comorbidities that may affect their patients and to provide appropriate intervention before these problems occur.

The endocrine system is highly sensitive to the effects of radiotherapy and chemotherapy, and the effects vary widely by sex and age of the patient and by treatment modality. Published reports do not always agree on some of the endocrinologic sequelae, and further studies will be needed to answer some of the lingering questions as well as to reaffirm early reports.

Unfortunately, no guidelines exist specifically for the endocrine effects of anticancer therapies, especially treatment-induced bone loss. The recent report from the Institute of Medicine, *From Cancer Patient to Cancer Survivor: Lost in Transition*,² calls for the improvement of existing guidelines and the adoption of new evidence-based ones to address existing and future therapy regimens.

Increased awareness of the potential endocrine effects of anticancer therapies will encourage physicians to recognize them early and provide appropriate intervention treatment so their cancer survivor patients can have a better chance of leading healthy and productive lives.



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Why Is Late Effects Detection So Critical?

More than 10.8 million people in the United States have survived a diagnosis of cancer, and more than 417,000 Texans survived a diagnosis within 10 years.¹ As cancer treatment becomes more effective, this number is only expected to grow.

Many cancer survivors suffer no ill effects following their treatment. Others, however, may experience a variety of problems even years after their treatment. It is critical that primary care physicians know what to expect when these patients return to their office for routine treatment.

Unfortunately, cancer survivorship has yet to be well represented in undergraduate medical school curriculum. According to the Institute of Medicine:

Cancer survivorship has yet to be well represented in undergraduate medical school curriculum and only a few schools currently offer courses or clerkships pertaining to cancer survivorship. Some medical schools have incorporated survivorship issues into their curriculum by including cancer survivors as “standardized patients” in what are referred to as “structured clinical instruction modules.”

According to a review of the curriculum for medical oncology in graduate medical education programs, only some of the required content areas relate to survivorship (e.g., knowledge of drug toxicity, rehabilitation, and psychosocial aspects of clinical management of the cancer patient). Generally, no specific mention is made of cancer survivorship.

All providers need to be apprised of the potential late effects of cancer treatment, the likelihood of cancer recurrence and secondary cancers, the benefits of added surveillance and interventions, discussion of psychosocial concerns, cancer prevention and lifestyle changes, and the difficulties with integrating survivorship concerns with other chronic conditions.²

1. Society AC. *Texas Cancer Facts & Figures*, American Cancer Society HPD, Inc., Editor. 2008: Austin, TX.

2. Institute of Medicine, Educating Cancer Health Professionals, Fact Sheet, November 2005.

Survivorship Medical Issues



Symptom Management

- Cancer-related fatigue
- Pain
- Sleep disturbances
- Stress disorder
- Cognitive dysfunction
- Sexual dysfunction
- Infertility



Comorbidity Management

- Cardiovascular
- Depression and anxiety
- Endocrine
- Gastrointestinal
- Infection
- Neurologic
- Psychiatric
- Pulmonary
- Renal
- Rheumatologic
- Skin



Healthy Living

- Smoking cessation
- Nutritional evaluation
- Medical evaluation for exercise program
- Physical therapy
- Occupational therapy
- Rehabilitation assessment
- Psychological assessment
- Genetic evaluation and counseling

Possible Late Effects of Radiation Therapy, Chemotherapy, and Hormonal Therapy Among Survivors of Adult Cancers²

Organ System/ Tissue	Possible Radiation Therapy Long-Term and Late Effects	Chemotherapy/Hormonal Therapy	
		Possible Long-Term and Late Effects	Agent Responsible
All tissues	Second cancers	Second cancers	Steroids, alkylating agents, nitrosoureas, topoisomerase inhibitors, anthracyclines
Bone and soft tissue	Atrophy, deformity, fibrosis, bone death	Bone death and destruction, risk of fractures	Steroids
Cardiovascular (heart)	Scarring or inflammation of the heart, coronary artery disease	Inflammation of the heart, congestive heart failure	Anthracyclines, high-dose cyclophosphamide, cisplatin, Herceptin, taxanes
Endocrine-pituitary (gland)	Various hormone deficiencies	Diabetes	Steroids
Endocrine-thyroid (gland)	Low thyroid function, thyroid nodules		
Endocrine-gonadal (gland)	Sterility Men: testosterone deficiency Women: premature menopause	Sterility Men: testosterone deficiency Women: premature menopause	Alkylating agents, procarbazine hydrochloride, nitrosoureas
Gastrointestinal (stomach)	Malabsorption, intestinal stricture	Motility disorders	Vinca drugs
Genitourinary	Bladder scarring, small bladder capacity	Hemorrhagic cystitis	Cyclophosphamide, ifosfamide, transplant therapy
Hematologic (blood)	Low blood counts, myelodysplastic syndrome, and acute leukemia	Myelodysplastic syndrome and acute leukemia	Alkylating agents, nitrosoureas, topoisomerase inhibitors, purine analogs, and high-dose therapy with autologous transplantation
Hepatic (liver)	Abnormal liver function, liver failure	Abnormal liver function, cirrhosis, liver failure	Methotrexate, carmustine (BCNU)
Immune system	Impaired immune function, immune suppression	Impaired immune function, immune suppression	Steroids, antithymocyte globulin (ATG), methotrexate, rituximab, alemtuzumab, purine analogs, and any high-dose therapy with autologous transplantation
Renal (kidney)	Hypertension, impaired kidney function	Impaired kidney function, delayed-onset renal failure	Cisplatin, methotrexate, nitrosoureas

Knowledge Assessment Questions

1. _____ and _____ are the preferred methods to treat malignancies affecting the hypothalamic-pituitary axis.
2. _____ is among the least-common observed pituitary disorders, but it can be the most serious.
 - A. Adrenocorticotropic hormone deficiency
 - B. Gonadotropin deficiency
 - C. Central hypothyroidism
3. **Certain chemotherapeutic agents such as cyclosporine and valproic acid have been reported to injure bone tissue.**
 - A. True
 - B. False
4. **The primary risk factor for ovarian failure following radiation regimen is _____.**
5. **The likelihood of hypothyroidism depends on the _____.**
 - A. Age of patient
 - B. Sex of patient
 - C. Type of treatment received

Please check the rating that best reflects how much you knew about each of the following areas before the course, and how much you know after this activity using the five-point scale.

1=Not at all knowledgeable 2=A little knowledge 3=Neutral 4=Some knowledge 5=Extremely knowledgeable

Cancer survivorship implications

- ___ Knowledge before activity
___ Knowledge after activity

Endocrine effects of anticancer therapy

- ___ Knowledge before activity
___ Knowledge after activity

Impact of radiation therapy on the skeletal system

- ___ Knowledge before activity
___ Knowledge after activity

Incidence of hypopituitarism, growth hormone deficiency, hyperprolactinemia, hypothyroidism, or gonadal dysfunction in patients who have undergone anticancer therapy

- ___ Knowledge before activity
___ Knowledge after activity

Answers:
1. Surgery, radiotherapy
2. A
3. True
4. Age
5. C

"Potential Endocrine Effects of Anticancer Therapy" Evaluation

Please rate each of the following aspects of the article by circling your response at the right.

	Strongly Agree	Agree	Disagree	Strongly Disagree
The content met objectives.	4	3	2	1
The content was free of commercial bias.	4	3	2	1
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Will this education improve the quality of patient care in your office?	Yes _____	No _____		

Given this information, what strategies would you employ if you suspected damage to the pituitary or thyroid glands due to anticancer therapy?

In order to receive continuing medical education credit for this activity, participants must submit the completed knowledge assessment, evaluation, and a payment of \$35. Items must be marked or faxed before the CME expiration date of June 1, 2012.

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Expiration: _____ Security Code: _____

Statement of completion: I attest to having completed the CME activity. (Check box.)

The time I spent was _____ hour(s), _____ minutes.

Signature: _____

Please return the self assessment, knowledge assessment, and evaluation forms to

Texas Medical Association, Attn: POEP, 401 W. 15th St., Austin, TX 78701; or fax to (512) 370-1693. Expiration date: June 1, 2012.



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