Hello. My name is Sai-Ching Jim Yeung. I am an Associate Professor in the General Internal Medicine Ambulatory Treatment and Emergency Care Department at MD Anderson Cancer Center. And ladies and gentleman, today, in this module of the Professional Oncology Education Series, I will talk about the Endocrine Issues in cancer survivors.

Who is a cancer survivor? Wikipedia says a cancer survivor is an individual with cancer of any type, current or past, who is still living. Another definition that I like that I found on the Internet, at this web site here, is anyone who has been diagnosed with cancer from diagnosis to end of life is considered a cancer survivor.

The endocrine issues involve many organs. This cartoon shows a list of endocrine organs and tissues in the human body and the endocrine systems are complex and are very important to the well-being of the person.

The issues about gonadal issues, bone will be covered elsewhere in different presentations by my colleagues. Today, I will restrict my presentation to issues about the thyroid, adrenal gland, hypothalamic and pituitary issues and that this will be discussed in Part A; and then in the second part of my presentation, I would talk about diabetes and obesity.

Hypothalamic and pituitary issues.

The hypothalamus and the pituitary gland are located in a very small area right behind the eyes. The hypothalamus is the command center and it controls the master gland, the pituitary, which is the interface between neurotransmission and endocrine signaling. Because of the strategic importance of this small amount of space in the body, damage to this area by tumor, by hemorrhage, such as an apoplexy, by surgery or radiation can result in significant morbidity or even mortality.

The anterior pituitary secretes two hormones, oxytocin and vasopressin, or anti-diuretic hormone. And compared with the posterior pituitary, the anterior pituitary is relatively not sensitive to radiation. However, surgery or tumors, for example, craniopharyngiomas, can cause dysfunction. And apart from childbirth or nursing, anterior pituitary dysfunction primarily manifests as a problem of free water balance. It ends up in this syndrome of inappropriate anti-diuretic hormone or SIADH or diabetes insipidus, the central type, due to the lack of anti-diuretic hormone. If the damage in that strategic location extends to the hypothalamic thirst center that controls the thirst and drinking behavior, the clinical management of the free water balance can be extremely challenging.

The posterior pituitary gland secretes many hormones, the growth hormone - somatotropin, adrenocorticotropin, thyroid stimulating hormone, or thyrotropin, or gonadotropins, luteinizing hormone and follicular stimulating hormone and prolactin. In addition to the susceptibility to damage by tumor, surgery or hemorrhage, the hypothalamus and the posterior pituitary gland are very sensitive to radiation. The radiation exposure can result in disruption and dysfunction of the hypothalamic posterior pituitary hormone axis frequently. And these charts here, this chart is showing the impact of radiation on growth hormone and this chart here is showing the impact of radiation on the adrenocorticotropin. The data came from different studies that are plotted on the same graphs and the amount of radiation and the site of the radiation, where it is aimed at is shown on this key here. Growth hormone secretion is most likely to be affected among all the posterior pituitary hormones. And at about five years after the radiation exposure, practically all the patients would have growth hormone dysfunction if the radiation is aimed at the pituitary. And about --- about 50% of the patients would have growth hormone dysfunction if the radiation is aimed at other areas in the head and neck. A similar pattern of radiation dose-dependent effect is seen with the adrenocorticotropin, although this hormone axis is less sensitive to radiation compared with growth hormone.

Surprisingly, the thyrotropic axis is not as sensitive and perhaps is the least sensitive axis among the pituitary hormones and the dose-dependent effect is not as apparent as the other axes. Here in this graph the impact of radiation on the gonadotropins, the luteinizing hormone and the follicular stimulating hormone is also shown here.

And in this graph here, the impact of radiation on prolactin is shown and again there appears to be a radiation dose-dependent effect.

Now overall, the most frequent cause of hypopituitarism in cancer survivors is radiation. Cancer survivors with hypopituitarism often would have a history of radiotherapy. The onset of dysfunction detectable by laboratory testing is insidious and is delayed in terms of years after radiotherapy. The signs and symptoms of hypopituitarism are nonspecific and very difficult to recognize. And clinicians must have a very high index of suspicion to test for hypopituitarism when considering the differential diagnosis of fatigue or failure-to-thrive in cancer survivors. The endocrinologists in our institution routinely screen cancer survivors with history of radiotherapy near the head.

Now adrenal dysfunction in cancer survivors includes hyperfunction and hypofunction. And hyperfunction can occur in the context of ACTH-secreting pituitary tumors or cancer-secreting ACTH ectopically and adrenocortical carcinomas.
The adrenal hypofunction is, by far, a much more common clinical problem encountered by clinicians and we shall devote more time to this topic.

For adrenal insufficiency, weakness, fatigue, nausea, vomiting and weight loss are the symptoms of hypoadrenalism, but they are nonspecific. Cachexia and weakness can mimic the general wasting of extensive metastatic disease and electrolyte abnormalities can easily be explained by poor intake, malnutrition, side effects of chemotherapy, etc. And the onset of symptoms are insidious, but an acute crisis usually precipitated by an acute event, is very likely to involve hypoglycemia and hypotension and can be life threatening.

As I have discussed earlier in the hypothalamic pituitary section, a history of radiotherapy to or near the head and neck area is associated with central hypoadrenalism.

There is a long list of events or factors that can precipitate an adrenal crisis. In immunocompromised cancer survivors, pyrogens and sepsis are important factors. And in terms of drugs, the imidazole antifungals are often used in immunocompromised cancer patients. And these other drugs here can also block glucocorticoid synthesis, but they are not commonly used drugs except for etomidate.

Primary adrenal failure can be caused by infection, infiltrative diseases, and loss of --- or damage to the adrenal tissue. Infection by my --- mycobacteria, fungi, yeast, and viruses can occur commonly in immunocompromised cancer survivors, for example patients with leukemia, lymphoma and bone marrow transplant patients. In cancer patients, metastatic disease that extensively replaces both adrenal glands can cause primary adrenal insufficiency. And secondary hemochromatosis can occur in patients with --- that are chronically dependent on transfusion, for example, in myelofibrosis. And myeloma can cause amyloidosis.

Some renal cancer patients can end up with bilateral adrenalectomy and thrombocytopenia is common among cancer patients that undergo chemotherapy or leukemia patients. And coagu --- coagulopathy can happen in patients with extensive liver metastasis. Disseminated intravascular coagulation is common in patients with acute promyelocytic leukemia.

Now this is a list of differential diagnoses for secondary adrenal failure. As mentioned earlier, radiation exposure, surgery and tumors can cause this problem and secondary hemo --- hemochromatosis due to chronic transfusion can damage the hypothalamic-pituitary axis. And many cancer survivors need therapy with glucocorticoids and functional suppression of the ACTH secretion by glucocorticoid therapy can occur for months after stopping the glucocorticoids and this by far is the very common clinical problem encountered in cancer survivors.

Next, I would discuss about thyroid problems, both hyperfunction and hypofunction.

Just a quick review of the regulation of thyroid hormones. Upon stimulation of the thyroid glands by thyrotropin, the thyroid gland secretes thyroid hormones in the form of thyroxine, T4, and triiodothyronine, T3. And in the peripheral tissue, T4 is converted to T3 and these hormones would reach the hypothalamus and the pituitary to provide a negative feedback, inhibiting the secretion of thyrotropic --- thyrotropin releasing hormone, which stimulates the release of thyrotropin or TSH. And the major mechanisms of dysfunction in cancer survivors are through radiation damage and autoimmune disease.

Thyrotoxicosis can be due to thyroiditis or injury to the thyroid or hypothyroidism. In cancer survivors radiation --- radiation exposure is often associated with thyrotoxicosis. Radiation can cause a thyroiditis. And then a silent thyroiditis with trans --- transient thyrotoxicosis and low/absent radioiodine uptake can occur in about 0.6% of Hodgkin's disease patients who receive external beam radiation. And most of cases would occur within two years of treatment and most cases are followed by hypothyroidism several months later. And Graves' disease is an autoimmune disease and it occurs in 3% to 7% of cancer patients with radiation exposure to the thyroid. And this again is most commonly seen in Hodgkin's disease patients and having the HLA B8 and DR5 haplotypes may increase the risk of having these autoimmune diseases.

Interferon-α2 and Interleukin-2 are drugs used in the immunotherapy of cancer. In one study, 3 out of 68 patients receiving Interferon-α2 had transient thyrotoxicosis and Graves' disease followed --- following transient thyrotoxicosis have also been reported. Interleukin-2 causes transient hyperthyroidism in 6% to 7% of the patients taking them, followed by hypothyroidism in half of these patients. And Interleukin-2 may induce the autoimmune destruction of the thyroid glands.

When severe thyrotoxicosis got out of control, a life-threatening condition of thyroid storm can occur. And thyroid storm primarily occurs in patients with untreated or inadequately treated Graves' disease. It also occurs in patients
with severe elevation of the β-human chorionic gonadotropin, in patients with trophoblastic tumors, hydatidiform moles and germ cell tumors. This is a severe hypometabolic and hypersympathetic state. And the signs and symptoms include high fever, tachycardia, diaphoresis, diarrhea, vomiting, confusion, delirium and coma. Burch and Wartofsky in 1993 published and proposed a scoring system for grading the thyrotoxicosis and diagnosing thyroid storm. And this is a very serious situation because it carries a mortality rate of 20% to 40%.

This is a list of factors that can precipitate a thyroid storm. The ones that are particularly relevant to cancer survivors are infection, especially among immunocompromised patients, intravenous contrast radiographic dye exposure, usually from CAT scans that the cancer patients often get, and pulmonary embolism, which frequently happens in cancer patients.

For the treatment of thyroid storm, beta-adrenergic blockade, inhibition of the thyroid hormone synthesis, and inhibition of thyroid hormone synthesis and release are the three main pillars of therapeutic intervention. With each category, there are choices of agents that can be used based on the availability and the clinician’s preference.

And in life-threatening cases, rapid removal of thyroid hormone from the circulation by plasmapheresis, charcoal plasma perfusion, or resin hemoperfusion may be considered. And supportive care will include intravenous fluid, oxygen, cooling blanket, antipyretics, antiemetics, corticosteroid, etc. The last but not least, we need to identify and treat the precipitating cause.

This table shows the probability of primary hypothyroidism after radiotherapy in several different studies with radiation aimed at different body sites. And you can see that Hodgkin's disease and head and neck cancer are high on the list here.

This study by Hancock et al. in Hodgkin's disease patients best illustrates the time course of development of hypothyroidism after radiotherapy as well as the dose-dependent effect of radiation. And you can see that when the cohort is divided by the different levels of radiation, the probability of hypothyroidism is different. And the people that received higher doses of radiation have a higher probability of becoming hyper --- hypothyroid.

As I mentioned earlier about the hypothalamic pituitary hormones, irradiation to the head and neck area may also cause dysfunction of the thyrotropic axis. And this is less susceptible to radiation damage than the rest of the pituitary hormone axes and the dose dependency of the radiation is not apparent.

When hypothyroidism --- hypothyroidism is very severe, acute events or factors can precipitate myxedema coma. This is a list of factors known to precipitate myxedema coma. And infection and narcotics are commonly encountered in the cancer survivors.

Some chemotherapy can cause hypothyroidism, but the evidence is not so clear compared to the impact of radiation. L-asparaginase can inhibit protein synthesis and in a study it appears to reduce the TSH response to the TRH or thyrotropin-releasing hormone. Increased incidence of hypothyroidism have been reported in several different combinations in chemotherapy regimens, but it is not clear whether any particular agents are major contributors to this problem.

Several chemotherapy agents affect the serum binding of thyroid hormones causing abnormal thyroid hormone levels without truly causing hypothyroidism. L-asparaginase as a protein synthesis inhibitor may inhibit the synthesis of albumin and thyroid hormone-binding globulin and decrease the total thyroxine level. 5-FU or fluorouracil increases the total T4 and T3 levels by increasing the serum thyroid hormone binding, but the patients are euthyroid and have normal T4 index and normal TSH. Mitotane increases the thyroid-binding globulin and increases the total T4 and T3 and the TSH would remain normal. Combined alkylating agents and podophyllin derivatives have been reported to slightly decrease the total T4 and thyroid binding globulin, but the patients are euthyroid with the normal TSH, T4/TBG ratio and reverse T3.

So, to conclude this part A of my presentation here are a few take home messages. Hypothyroidism and primary hypothyroidism --- Hypopituitarism and primary hypothyroidism are common long-term complications of radiotherapy. Glucocorticoid therapy is a common cause of secondary adrenal insufficiency. Fungal and thyroid infections can
cause primary adrenal insufficiency in immunocompromised cancer patients. And immunotherapy can exacerbate autoimmune thyroid diseases.