# Endocrine Effects of Cancer Treatment

Dr. Walter Woznick

Division of Endocrinology

Medical College of Wisconsin

# Disclosures

None

# Objectives

1. Introduction
2. Mechanism of cancer therapy induced damage
3. Endocrine systems approach to pathophysiology, patient population at risk, diagnosis, treatment and follow-up
4. Special considerations – immunochemotherapies
5. Conclusion/Discussion

# Introduction

Therapy-related effects of cancer treatment have increasingly been recognized as patient survival improves. Endocrinopathies are among the most common observed effects.

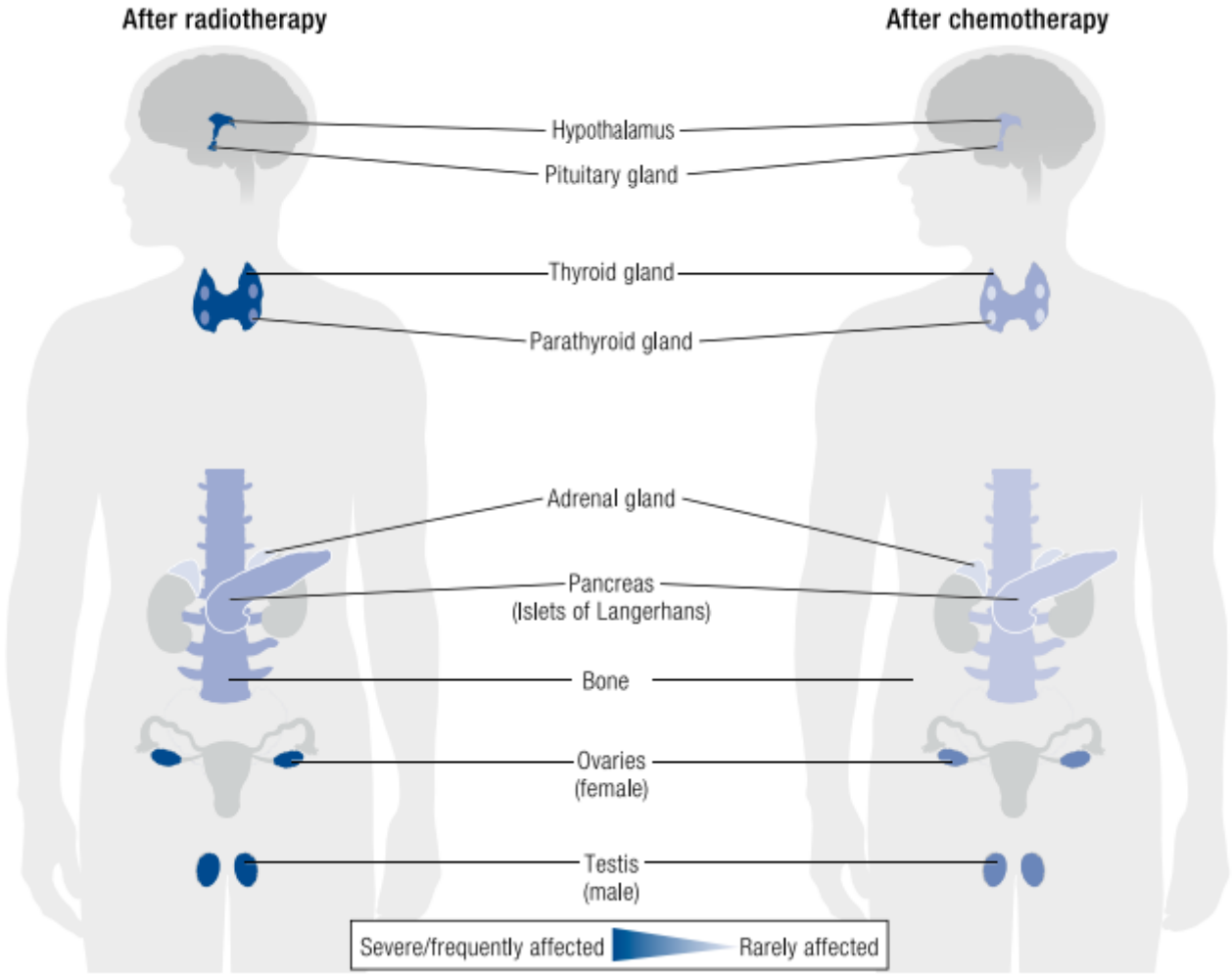
There is a significant body of data regarding the late therapy-related effects in children, but in adults, the data is less robust and is emerging with new treatments and longer survival.

Endocrine sequelae of cancer therapy include functional alterations in hypothalamic-pituitary, thyroid, parathyroid, adrenal, and gonadal regulation as well as bone and metabolic complications. Surgery, radiotherapy, chemotherapy, and immunotherapy all contribute to these sequelae.

# Mechanisms of Therapy Induced Damage

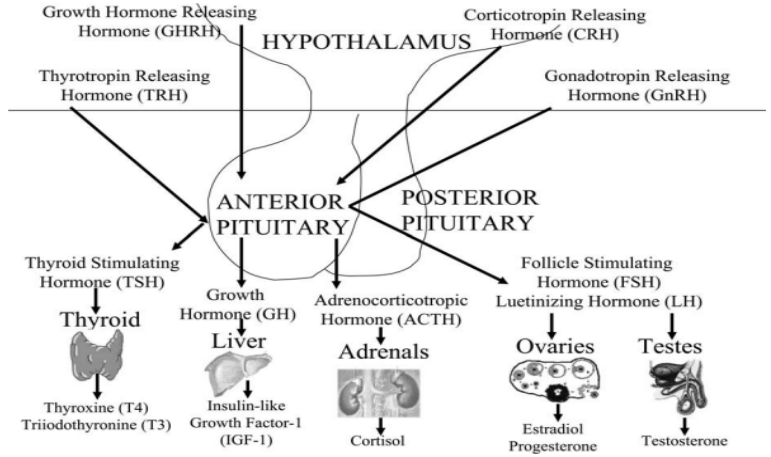
1. Surgery
   - Physical removal of Endocrine organ causing complete or partial loss of function
   - Damage to nearby Endocrine structures
2. Radiation
   - Multifactorial mechanisms related to radiation schedule, dose and type as well as age and sex of the patient. Effects may not be seen for decades after (thyroid and pituitary)
   - Direct radiation causes DNA damage, genomic instability and transformation
   - “Bystander effects” occur through scatter of ionizing radiation to non-target organs
3. Chemotherapy – Associated with acute and late onset complications
   - Mediated through DNA damage and oxidative stress on non-target cells
4. Immunotherapy
   - Newer therapies that result in immune mediated destruction of cancer cells and endocrine organs. Thyroid, pituitary, pancreas and adrenal glands are particularly sensitive.

**Figure 1.** Susceptibility of endocrine organs for late complications after radiotherapy or chemotherapy, graded from severe/frequently affected (darkest blue) to rarely affected (lightest blue).




Endocrine Reviews, June 2019, 40(3):711–767

# Hypothalamic-Pituitary Axis

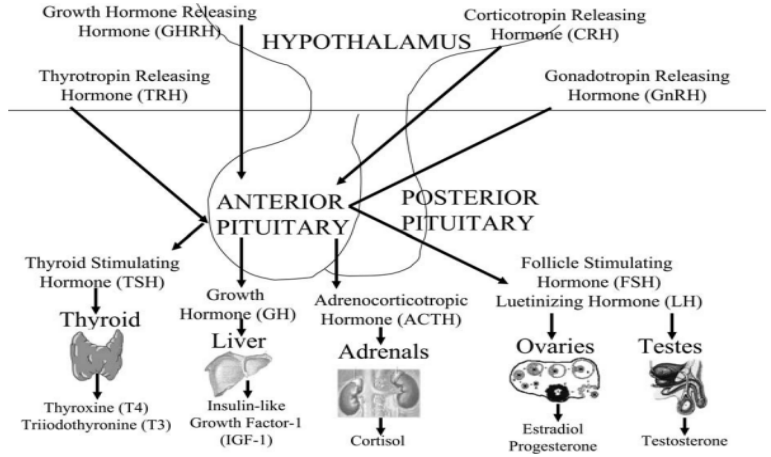


European Journal of Epidemiology (2006) 21: 217–226

**Pathophysiology**

1. Surgical effects from direct damage of the surgery or mass from the tumor itself.
2. Radiation effects - mostly effect anterior pituitary hormones. More than half of patient treated with cranial radiation experience at least 1 pituitary hormone deficiency at 25 years later. Ionizing radiation ≥ 30 Gy more likely to produce panhypopituitarism.
3. Chemotherapy – minimal case reports of chemotherapy damage to pituitary structures, no clear associations
4. Immunotherapy – growing body of evidence regarding effects of PD-1, PDL1 and CTLA-4 on Hypothalamic-pituitary function.

# Hypothalamic-Pituitary Axis

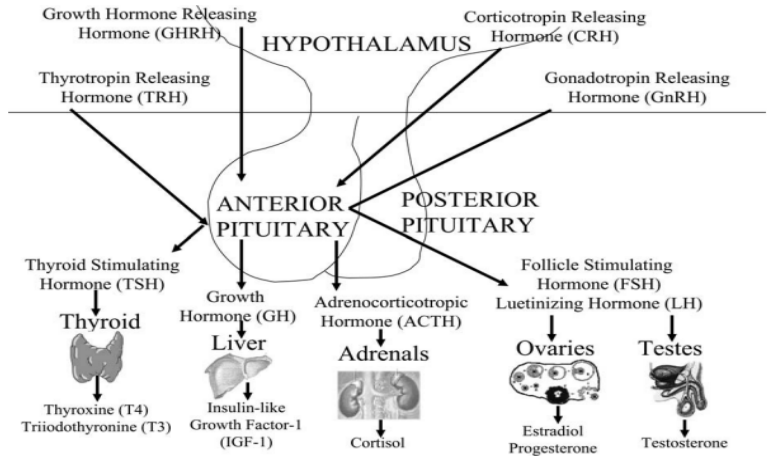


European Journal of Epidemiology (2006) 21: 217–226

**Pathophysiology – Radiation**

- GH – Most common deficiency from radiation (~30% in adults and as high as 50-100% in children) with either complete or partial deficiency (low radiation doses under 30 Gy)
- Central Hypogonadism – occurs in ~35% of patients receiving cranial radiation. In childhood, can result in activation and precocious puberty.
- Prolactin – normally under tonic inhibition from dopamine, when there is disruption from the dopaminergic neuron in the hypothalamus, prolactin levels rise. Low prolactin is rare and typically a sign of panhypopituitarism

# Hypothalamic-Pituitary Axis



European Journal of Epidemiology (2006) 21: 217–226

**Pathophysiology – Radiation**

- Central Adrenal insufficiency - ACTH deficiency, life threatening. Can occur in up to 30% of patient who have had cranial radiation.
- Central Hypothyroidism – TSH deficiency. Rare, occurring in about 10% of patients. If suspected, glucocorticoid deficiency must be ruled out or administered prior to thyroid hormone.

Non-pituitary brain tumors can produce HPA dysfunction in upwards of 65-90% of patients with radiation doses ≥ 50 Gy

# Hypothalamic-Pituitary Axis

**Patient population at Risk:**

- Adult primary brain tumor patient.
- Head and neck cancer treatment can also produce treatment-related late effects (bystander effect).

**Diagnosis:**

- Testing base on symptoms, vital signs and incidental lab findings. Can be difficult to delineate from normal effects of cancer treatment and in the case of radiation therapies, require a high index of suspicion as onset of symptoms are often decades later.

# Hypothalamic-Pituitary Axis

| Hormone | Symptoms | Imaging | Incidental findings | Diagnostic labs | Notes |
|---|---|---|---|---|---|
| LH/FSH | Male – hypogonadism<br>Women – POI | Normal pituitary, atrophy, partial or complete empty sella | Male – ED, low libido, low energy, gynecomastia/breast tenderness<br>Women – early menopause, prior to 40 yo, absence of menstruation for 12 months, irregular cycles, hot-flashes, vaginal atrophy/dryness | Measurement of LH/FSH and either estradiol levels or testosterone as appropriate.<br>*** Must be drawn as AM (between 0800 and 0900) and fasting labs** | SHBG and prolactin levels should be considered in the diagnosis. |
| ACTH | Hypotension, weight loss, generalized body ache (flu-like), weakness, nausea, vomiting, salt craving, low energy, low body temp | Normal pituitary, atrophy, partial or complete empty sella | Hyponatremia, hypoglycemia, microcytic anemia.<br>Usually have evidence of 1 other pituitary hormone | AM ACTH and cortisol or Cosyntropin stimulation testing. DHEAs can be used as an indicator of central AI<br>Random cortisol, if low or borderline is of little utility | *Life threatening. If suspected, give a stress dose steroid, Hydrocortisone 100 mg IV after drawing labs if possible |
| TSH | Low energy, weakness, cold intolerance, constipation, bradycardia, hypotension, body aches | Normal pituitary, atrophy, partial or complete empty sella | Usually have evidence of 1 other pituitary hormone | TSH, FT4. Occasionally can obtain FT3. | Life Threatening. MUST have a high index of suspicion for central hypothyroidism. TSH alone are usually normal. MUST rule out/treat Adrenal insufficiency first |
| Prolactin | Male – hypogonadism, rarely nipple discharge<br>Female – menstrual irregularities or amenorrhea, breast tenderness or galactorrhea | Normal pituitary, atrophy, partial or complete empty sella.<br><br>May find pituitary mass lesion with elevation; apoplexy w/deficiency. | Initial findings may consist of hypogonadal, mass lesion on prior head imaging, nipple discharge, peripheral vision disturbances with large lesion. SSRI/dopa antagonists (anti-psychotics) | AM, fasting prolactin level. | If low prolactin – evaluation for panhypopituitarism, obtain MRI.<br>Mild elevation between ULN and 100, consider dilution.<br>Prolactin >200 diagnostic<br>Rule out hypothryoidism |
| Growth Hormone | Obesity, fatigue, reduced muscle mass, poor mood, reduced quality of life | Normal pituitary, atrophy, partial or complete empty sella | Higher index of suspicion with more than 2 other hormone deficiencies | IGF-1 levels on multiple occasions.<br><br>Diagnosis confirmed with macimorelin or glucagon stimulation testing. Gold standard used to be insulin induced hypoglycemia. | Artificially low IGF-1 seen in poorly controlled diabetes, liver disease, and oral estrogen therapy |
| Vasopressin (ADH or AVP) | Polyuria (>3L per 24 hr)<br>Hypernatremia | Normal pituitary, atrophy, partial or complete empty sella<br><br>Can also see stalk thickening/abnormalities | High sodium, high serum osm, low urine specific gravity, inappropriate urine osm to serum osm. | Hypernatremia in the setting of inappropriate low urine specific gravity or urine osm | In the acute phase, central DI can be triphasic. 1. Initial destruction of hypothalamic neurons (low ADH – first 4-5 days). 2. Transient SIADH, hyponatremia (day 5-6), leak of ADH from damaged neurons 3. Chronic DI |

# Hypothalamic-Pituitary Axis

**Treatment:**

- Replacement of deficient hormone. In the case of hypothyroidism, must evaluate for adrenal insufficiency (to avoid adrenal crisis).
- When central hypothyroidism is treated, FT4 levels are used to monitor therapy as TSH is not a reliable marker.
- GH replacement will accelerate T4 to T3 conversion so T4 should be monitored closely with concomitant deficiency of GH and thyroid hormone
- GH treatment in adults remains controversial
- Testosterone therapy is indicated in males to prevent osteoporosis and cardiovascular comorbidities
- Estrogen therapy and progesterone (in women with an intact uterus) is indicated up to the normal time of menopause. Menopause hormone therapy can be considered thereafter in appropriate cases
- Patients with symptomatic elevation to prolactin are treated with dopamine agonists (cabergoline or bromocriptine)

# Hypothalamic-Pituitary Axis

**Monitoring:**

- For patients that have had brain, head or neck radiation a pituitary assessment should occur for at least 1-3 years intervals for high-risk patient ≥ 30 Gy and lifelong surveillance should be the standard as sequalae occur decades after treatment
- Cranial radiation is a risk for the development of primary brain tumors and pituitary neoplasm. Brain imaging should be obtained for any new endocrinopathy in patients with a hx of cranial radiation

# Thyroid

## Pathophysiology

- Radiation exposure to the head, neck or upper chest can damage the thyroid gland resulting in primary hypothyroidism (thyroid gland dysfunction with elevated TSH).
- Pre-existing or acquired thyroid auto-immunity increases the risk of radiation thyroid dysfunction.
- Chemo alkylating agents can cause thyroid damage
- Many tyrosine kinase inhibitors have been associated with primary hypothyroidism
- Patients who have received radioactive iodine may be at an increased risk for development of solid tumor cancer, breast cancer, uterine cancer and leukemias. (Mixed data on this topic)

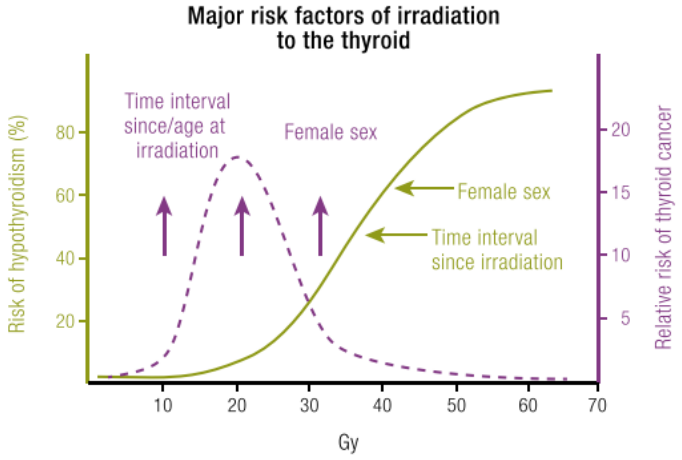



**Figure 2.** Major risk factors of irradiation to the thyroid. Arrows indicate shift of peak effect by the indicated regulators. [Includes data from Bhatti P, Veiga LH, Ronckers CM, et al. Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study. Radiat Res. 2010;174:741–752; and from Vogelius IR, Bentzen SM, Maraldo MV, et al. Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. Cancer. 2011;117:5250–5260.]

# Thyroid

## Patient Population at Risk

- Elevated risk for hypothyroidism in former breast cancer patient including patients >65 years of age (regardless or radiation)
- Patients with nasopharyngeal carcinoma, head and neck tumors who received radiation or surgery are at risk of hypothyroidism
- Allogenic HSCT patients should be monitored for hypothyroidism
- Patient who received ionizing radiation to the thyroid had an increased risk of thyroid cancer with a peak incidence around 20 Gy and higher risk for longer time interval after exposure and females
- Patients who have received alkylating agents (RR = 3.25), anthracyclines (RR = 4.5) and bleomycin (RR = 3.2) are at an increased risk of thyroid cancer
- Patients with primary Hodgkin and non-Hodgkin lymphoma, prostate, breast, HCC, gastric cancer as well as HSCT were at elevated risk for secondary thyroid cancer.

# Thyroid

**Diagnosis**

- Hypothyroidism - measurement of TSH and FT4. In the event of hypothyroidism, thyroid antibody testing would not be indicated. Could consider evaluation of TSI, TSH receptor antibodies, TPO or anti-thyroglobulin in hyperthyroid patients
- Thyroid cancer – if palpable nodules are appreciated on exam, thyroid ultrasound should be obtained.  FNA can be pursued in the event a nodule that has high enough suspicion and meets size criteria (included in thyroid ultrasound reports at Froedtert).
- In general, screening ultrasound is not recommended due to the vast majority of nodule being benign and significant comorbidities resulting from workup.

# Thyroid

**Treatment**

- Thyroid hormone replacement with levothyroxine. Rarely is T3 (liothyronine) indicated. There are no desiccated thyroid hormone products that are FDA approved or recommended in current medical guidelines (e.g., armor thyroid, NP thyroid, etc.).
- Thyroid hormone levels should be assessed every 6-12 months or 4-6 weeks with dose adjustment.
- Dose adjustment should be made in 10-15% intervals unless severe abnormalities noted.
- Full replacement weight-based dosing can be estimated by weight (kg) * 1.6.
- Careful consideration given to Goal TSH (between ~2.5 and 7 in elderly) and comorbidities (cardiac hx or who have received cardiotoxic chemotherapy, bone disease, pregnancy, adrenal insufficiency)

# Adrenal Glands

## Pathophysiology

- Adrenal insufficiency is a life-threatening disease that needs to be identified and treated immediately
- Peripheral adrenal insufficiency (primary adrenal insufficiency) results from acute destruction or removal of both adrenal glands or in patients after steroid synthesis inhibitor
- Treatment with high dose steroids (~7.5 mg prednisone equivalents or higher for over 3 months) present with significant complications and symptoms of excess cortisol – pseudo cushing's. Patient should be monitored for adrenal insufficiency after long-term glucocorticoid use has tapered to a stop.
- Treatment with long-term (years) opioids can also result in central adrenal insufficiency
- No clear association with specific chemotherapies and adrenal insufficiency

# Adrenal Glands

## Patient Population at Risk

- Survivors of head and neck cancers and patient with primary pituitary tumors are at increased risk for central adrenal insufficiency
- Patients with bilateral adrenal metastatic disease from primary cancer are also at risk for developing primary adrenal insufficiency
- Patient who have undergone nephrectomy. Pay close attention to final operative reports to look for adrenal tissue.

# Adrenal Glands

## Diagnosis

- If a patient is not currently in adrenal crisis, an 8 am, fasting cortisol and ACTH can be obtained as a screening test.
- Cosyntropin stimulation testing is the standard for full evaluation of the HPA axis. If completed in the AM, baseline cortisol and ACTH levels are helpful to determine non-stimulated function. ACTH and cortisol should be drawn at baseline regardless of time of day and this test can be complete at any point in the day. Stimulate cortisol levels should be >15 mcg/dL in 30-60 mins
- AM, fasting cortisol levels <3 mcg/dL is suggestive of AI. Cortisol levels >15 mcg/dL suggestive of normal adrenal function.
- ***Patient should be sufficiently removed from last steroid dose (at least 48-36 hrs) – dexamethasone in chemo treatments.**
- Consideration for DHEAs measurement should be given in select patients
- Patient at risk for central AI should be monitored yearly

# Gonadal Dysfunction

## Pathophysiology

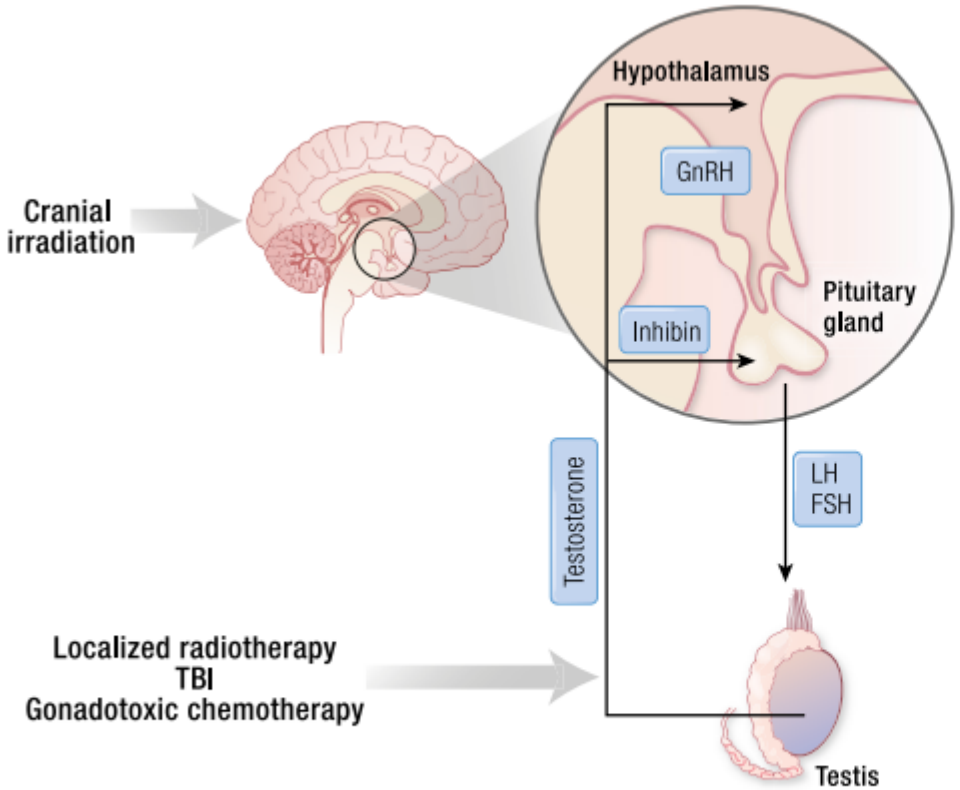
- Late gonadal effects in **males** – results from treatment with surgery (bilateral or unilateral orchiectomy), chemotherapy or radiation.
- Majority of toxicity occurs to either the germ cells or Leydig cells or a combination of both
- Leydig cell damage results in androgen deficiency.
- Highest risk for dysfunction comes from combination therapy with chemotherapy and radiation treatment. Patient should be counselled accordingly before treatment for family planning.

**Table 2.** Risk Categories of Gonadal Toxicity of Various Antineoplastic Agents in Male Patients With Cancer

| | Gonadotoxicity in Male Patients With Cancer | |
|---|---|---|
| | **Agents** | **Gonadotoxic Doses** |
| High risk | Mechlorethamine | |
| | Cyclophosphamide | >200 mg/kg in prepubertal males, >100 mg/kg in adults (320, 321); highest risk for permanent azoospermia: >6 g/m$^2$ or >7.5 g/m$^2$ (322, 323) |
| | Chlorambucil | >400 mg: highest risk for irreversible azoospermia in adult men (324) |
| | Carmustine, lomustine | |
| | Busulphan, melphalan | |
| | Procarbazine | |
| Medium risk | Cisplatin | >400 mg/m$^2$: permanent infertility in 50% of adult men, lower doses: long-term impaired fertility (325) |
| | Cytosine arabinoside | |
| | Doxorubicin | |
| | Daunorubicin | |
| | Methotrexate | |
| Low risk | Vincristine | |
| | Vinblastine | |
| | Prednisone | |
| | 5-Mercaptopurin | |

[Includes data from Oeffinger KC, Adams-Huet B, Victor RG, et al. Insulin resistance and risk factors for cardiovascular disease in young adult survivors of childhood acute lymphoblastic leukemia. J Clin Oncol. 2009;27:3698–3704; and from Oeffinger KC, Mertens AC, Sklar CA, et al. Childhood Cancer Survivors. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355:1572–1582.]

# Gonadal Dysfunction




**Radiation exposure of hypothalamus and pituitary:**
- Precocious puberty
- Early-normal puberty
- Pubertas tarda
- Hypogonadotrophic hypogonadism

**Radiation exposure of testes:**
- Oligospermia
- Azoospermia
- Pubertas tarda
- Hypergonadotrophic hypogonadism

**Gonadotoxic agents:**
- Oligospermia
- Azoospermia
- *in rare cases* pubertas tarda and hypergonadotrophic hypogonadism

**Figure 3.** Disorders of pubertal development, hypogonadism, and infertility in male patients following antineoplastic therapy.

Endocrine Reviews, June 2019, 40(3):711–767

# Gonadal Dysfunction

## Pathophysiology

- Late gonadal effects in **Females** – Premature ovarian failure (POF) results from estrogen deficiency and germ cell damage and ultimately infertility. Again, most of the toxic effects are related to chemotherapy and radiation
- Highest risk to POF and amenorrhea occur with alkylating agents and increased age.
- Most likely offending treatment regimens coming from Hodgkin's disease, non-Hodgkin's disease, breast cancer and gastrointestinal cancer.

**Table 3.** Risk Categories of Gonadal Toxicity of Various Antineoplastic Agents in Female Patients With Cancer

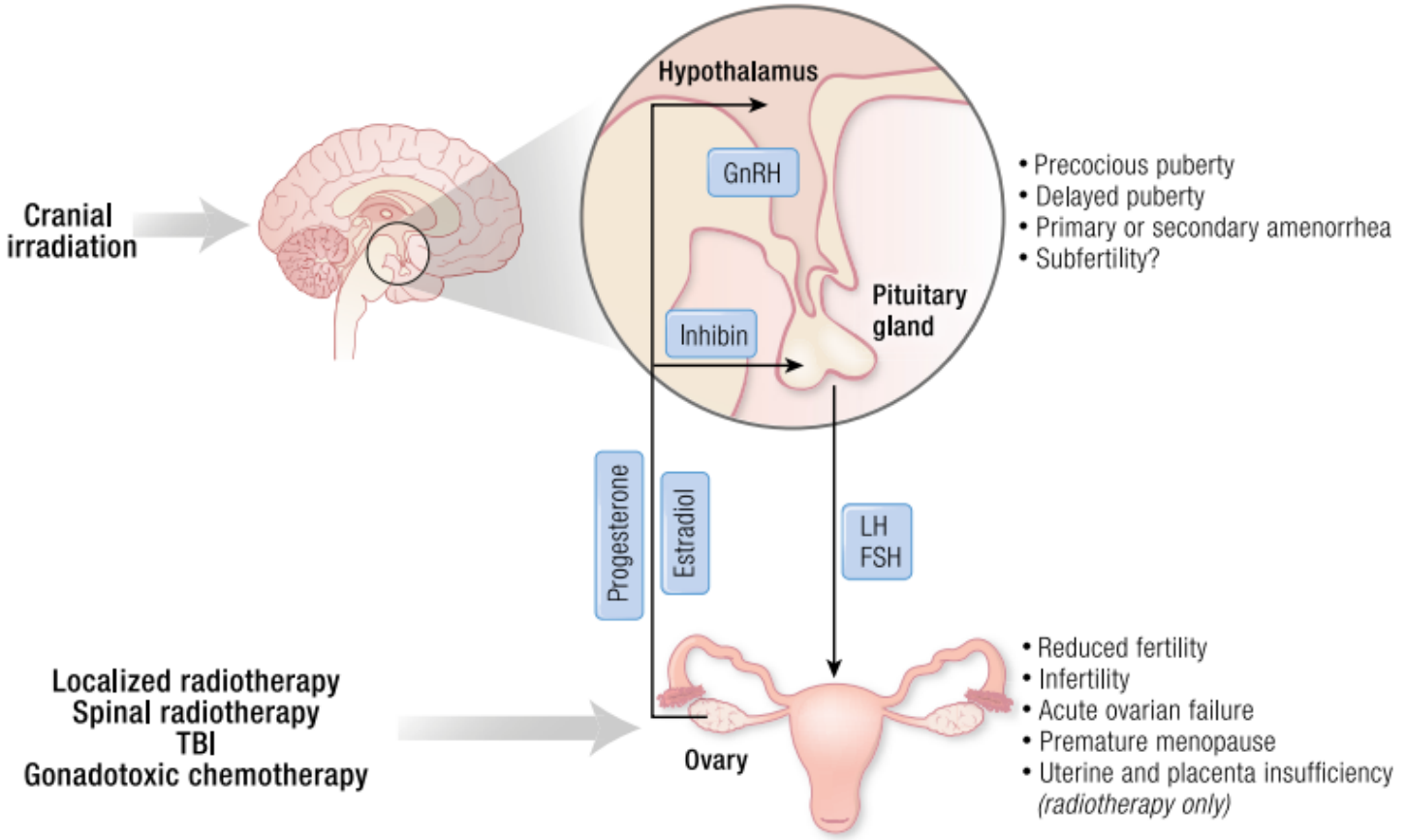
| | Gonadotoxicity in Female Patients With Cancer | |
|---|---|---|
| | **Class** | **Agents** |
| High risk | Alkylating agents | Mechlorethamine |
| | | Cyclophosphamide |
| | | Chlorambucil |
| | | Melphalan |
| | | Busulphan |
| | Nonclassic alkylators | Procarbazine |
| | | Dacarbazine |
| Medium risk | Heavy metals | *Cis*-platinum |
| | Antimetabolites | Cytosine arabinoside |
| | Anthracyclines | Doxorubicin |
| | Podophyllotoxins | Ttopsoide (VP-16) |
| | Alkylating agents | Carmustine, lomustine |
| | Vinca alkaloids | Vinblastine |
| Low risk | Antimetabolites | Methotrexate |
| | | 5-Fluorouracil |
| | | 6-Mercaptopurine |
| | Vinca alkaloids | Vincristine |
| | Antibiotics/alkylating agents | Mitomycin |

[Includes data from Oeffinger KC, Adams-Huet B, Victor RG, et al. Insulin resistance and risk factors for cardiovascular disease in young adult survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 2009;27:3698-3704; and from Oeffinger KC, Mertens AC, Sklar CA, et al. Childhood Cancer Survivors. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-1582.]

Endocrine Reviews, June 2019, 40(3):711–767

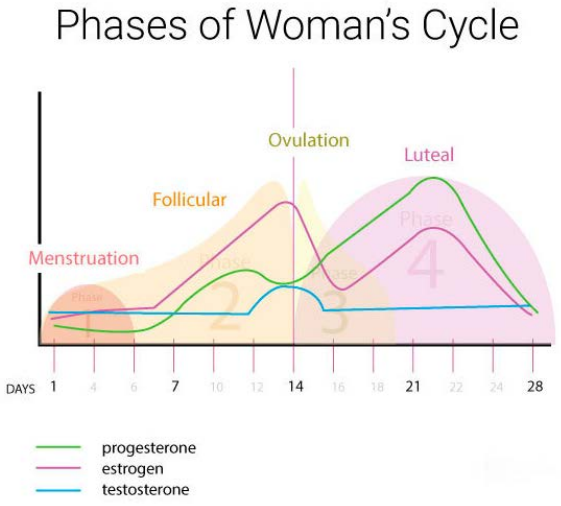
# Gonadal Dysfunction

**Figure 4.** Disorders of pubertal development, hypogonadism, infertility, and uterine function in female patients following antineoplastic therapy. [Includes data from De Bruin ML, Van Dulmen-den Broeder E, Van den Berg MH, Lambalk CB. Fertility in female childhood cancer survivors. Endocr Dev 2009; 15:135-158.]



# Gonadal Dysfunction

- Diagnosis
  - **In Males** - should be made with a high suspicion in any patient that has been exposed to radiation to the testis or alkylating agents. Symptoms would include loss of libido, decreased AM erections or erectile dysfunction, loss of muscle mass, hot flashes, loss of body hair or shrinking testis.
  - AM (between 0800 and 0900) and fasting testosterone (free and total), SHBG, LH and FSH should be obtained.
  - **In Females** – again, consider the cancer treatment history as well as sexual side effects; low libido, vaginal dryness, dyspareunia, postcoital bleeding. Should also consider potential galactorrhea, signs of virilization and menstrual irregularities.
  - When evidence suggests gonadal dysfunction, LH, FSH and estradiol levels should be assessed and luteal phase progesterone. With amenorrhea or infertility, early follicular phase estradiol, FSH, prolactin and testosterone levels should be obtained. FSH >10 in the early phase implies POF. AMH can be helpful as well (low in POF).



# Gonadal Dysfunction

- Treatment
  - **In Males** – Testosterone replacement following standard guidelines. In patient who have had prostate cancer or other androgen sensitive tumors; it is not necessarily contraindicated to start testosterone after a discussion of risks and benefits. Cryopreservation should be considered before cancer treatment
  - **In Females** – Estrogen therapy with progesterone (intact uterus) should be considered, but robust data is lacking with respect to dosing and duration. Estrogen therapy is generally not given to women with estrogen sensitive tumors. Therapy can be transitioned to a menopause hormone therapy around the age of 50. If estrogen therapy is not given in POF, bone protection should be pursued.

Any fertility issues should ideally be addressed by a fertility expert, Gynecology and Endocrinology and/or Reproductive Endocrinology

# Immunochemotherapies

**Three main classes**
PD-1, PDL1 and CTLA-4

Ipilimumab was the first of the immune-checkpoint inhibitors on the market since 2011.

| Drug | Brand name | Indication |
|---|---|---|
| CTLA-4 blockers | | |
| Ipilimumab | Yervoy | As monotherapy for metastatic melanoma and surgically resectable 'high-risk' melanoma (adjuvant setting) |
| PD-1 blockers | | |
| Nivolumab | Opdivo | Metastatic melanoma, metastatic non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin's lymphoma, head and neck squamous cell carcinoma (HNSCC), metastatic urothelial carcinoma, hepatocellular carcinoma (HCC), colorectal cancer with MSI-H and MMR aberrations |
| Pembrolizumab | Keytruda | Metastatic melanoma, surgically resectable 'high-risk melanoma (adjuvant setting), metastatic NSCLC, classical Hodgkin's lymphoma, primary mediastinal B-cell lymphoma (PMBCL), HNSCC, gastric cancer, solid tumors with MSI-H and MMR aberrations, metastatic urothelial carcinoma, Merkel cell carcinoma, renal cell carcinoma, cervical cancer, hepatocellular carcinoma, |
| Cemiplimab | Libtayo | Metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation |
| PD-L1 blockers | | |
| Atezolizumab | Tecentriq | Metastatic urothelial carcinoma, metastatic NSCLC (monotherapy and in combination with chemotherapy), metastatic SCLC (in combination with chemotherapy) and metastatic triple negative breast cancer (in combination with paclitaxel) |
| Avelumab | Bevencio | Merkel cell carcinoma, metastatic urothelial carcinoma |
| Durvalumab | Imfinzi | Metastatic urothelial carcinoma, unresectable stage III NSCLC |
| Combination of CTLA-4 and PD-1 blockers | | |
| Ipilimumab plus nivolumab | Yervoy plus Opdivo | Metastatic melanoma, metastatic renal cell carcinoma, colorectal cancer with MSI-H and MMR aberrations |

Rotte Journal of Experimental & Clinical Cancer Research (2019) 38:255

## PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE-CHECKPOINT INHIBITORS

| Pre-Therapy Assessment[a] | Monitoring Frequency[b] | Evaluation for Abnormal Findings/Symptoms |
|---|---|---|
| **Clinical**<br>• Physical examination<br>• Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease<br>• Neurologic examination<br>• Bowel habits (typical frequency/consistency)<br>• Infectious disease screening (HIV; hepatitis A, B, C) as indicated | Clinical exam at each visit with adverse event (AE) symptom assessment | Follow-up testing based on findings, symptoms |
| **Imaging**<br>• Cross-sectional imaging<br>• Brain MRI if indicated | Periodic imaging as indicated | Follow-up testing as indicated based on imaging findings |
| **General bloodwork**<br>• CBC (with differential if indicated)<br>• Comprehensive metabolic panel | Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated | HbA1c for elevated glucose |
| **Dermatologic (ICI_DERM-1)**<br>• Examination of skin and mucosa if history of immune-related skin disorder | Conduct/repeat as needed based on symptoms | Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated. |
| **Pancreatic (ICI_ENDO-1)**<br>• Baseline testing is not required. | No routine monitoring needed if asymptomatic | Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis. |
| **Thyroid (ICI_ENDO-2)**<br>• Thyroid-stimulating hormone (TSH), free thyroxine (T4)[c] | Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated | Total T3 and free T4 if abnormal thyroid function suspected. |
| **Pituitary/Adrenal (ICI_ENDO-3)**<br>• Consider serum cortisol (morning preferred) and thyroid function as above | Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6–12 weeks as indicated | Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (males), estradiol (females), adrenocorticotropic hormone (ACTH), and serum cortisol |
| **Pulmonary (ICI_PULM-1)**<br>• Oxygen saturation (resting and with ambulation)<br>• Consider pulmonary function tests (PFTs) with diffusion capacity for high-risk patients (eg, interstitial lung disease on imaging, COPD, previous suspected treatment-related lung toxicity) | Repeat oxygen saturation tests based on symptoms | Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes. |
| **Cardiovascular (ICI_CARDIO-1)**<br>• Consider baseline ECG<br>• Individualized assessment in consultation with cardiology as indicated | Consider periodic testing for those with abnormal baseline or symptoms | Individualized follow-up in consultation with cardiology as indicated |
| **Musculoskeletal (ICI_MS-1)**<br>• Joint examination/functional assessment as needed for patients with pre-existing disease | No routine monitoring needed if asymptomatic | Consider rheumatology referral.<br>Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine phosphokinase (CPK) |

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B). For disease-specific COVID-19 recommendations, see the NCCN COVID-19 Resource page.

[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

# Immunochemotherapies

- Most common complication is primary hypothyroidism. Adrenal insufficiency (secondary or primary), hypophysitis, central hypothyroidism, type 1 diabetes are also seen.
- Endocrinopathies typically manifest between 6 weeks to 6 months after initiation of therapy to the last dose of therapy.
- It is important to rule out adrenal insufficiency prior to any thyroid hormone replacement – failure to do this can result in adrenal crisis. **Symptoms are often overlapping and presence of one deficiency does not preclude another deficiency.**
- Once the damage has occurred, it is unlikely to recover function after discontinuation of the medication.
- Glucocorticoid therapy in patients with adrenal insufficiency does not interfere with continued immunochemotherapy

# Immunochemotherapies

- TSH, FT4, AM cortisol, AM ACTH, BMP and in select cases pituitary hormones should be obtained at the initiation of therapy and every 4-6 weeks during therapy.
- In evaluating cortisol levels, this should be completed fasting between 0800 and 0900 and chart should be reviewed so as not to draw a blood level within 36 hr of last glucocorticoid dosing
- Normal TSH and low FT4/FT3 should be carefully assessed for central hypothyroidism.
- If a single hormone deficiency is found in ACTH or TSH, a full pituitary hormone evaluation should be completed.

# Conclusion

- In evaluating cancer survivors, careful consideration needs to be given to treatment regimen and later endocrine complications.
- External beam radiation should always be considered as a risk to endocrine gland and effects are typically not seen for decades later.
- Treatment generally consists of hormone replacement. Care needs to be given with hypothyroidism that concomitant adrenal insufficiency has been ruled out.
- Careful consideration should be given to any patient who receives an immunochemotherapy (checkpoint inhibitor) to monitor for thyroid, adrenal disorders and diabetes.

# References

1. Endocrine Reviews, June 2019, 40(3):711–767

**Table 5. Important References and Guidelines for Patient Management and Treatment**

| |
|---|
| **Long-term follow-up guidelines** |
| • COG: Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers (3) |
| • Late effects surveillance recommendations among survivors of childhood HSCT: a Children's Oncology Group report by Chow *et al.* (657) |
| • PDQ Pediatric Treatment Editorial Board: Late effects of treatment of childhood cancer (PDQ®): health professional version (298) |
| • SIGN: Long term follow-up of survivors of childhood cancer (5) |
| • DCOG/SKION: Guidelines for follow-up in survivors of childhood cancer 5 years after diagnosis (7) |
| • S3 Guideline: "Endokrinologische Nachsorge nach onkologischen Erkrankungen im Kindes- und Jugendalter" (only available in German) (4) |
| Thyroid complications |
| • Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium by Clement *et al.* (198) |
| • Current recommendations in the management of hypothyroidism: developed from a statement by the British Thyroid Association Executive by Paretti *et al.* (181) |
| HP complications |
| • Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline by Fleseriu *et al.* (72) |
| Gonadal complications |
| • Recommendations for gonadotoxicity surveillance in male childhood, adolescent and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium by Skinner *et al.* (313) |
| • Recommendations for premature ovarian insufficiency surveillance for female childhood, adolescent and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium by van Dorp *et al.* (368) |
| • Survivorship, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology (Recommendations for screening, evaluation, and treatment of sexual dysfunction and menopausal symptoms in male and female survivors of adult cancer) by Denlinger *et al.* (667) |
| • Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline by Bhasin *et al.* (109) |
| Metabolic complications/healthpromotion |
| • National Comprehensive Cancer Network: Survivorship: healthy lifestyles, version 2.2014 by Denlinger *et al.* (668) |
| • National Comprehensive Cancer Network: Survivorship: nutrition and weight management, version 2.2014 by Denlinger *et al.* (669) |
| • Nutrition and physical activity guidelines for cancer survivors by Rock *et al.* (612) |
| • Metabolic syndrome and cardiovascular disease after HSCT: screening and preventive practice recommendations from the CIBMTR and EBMT by DeFilip *et al.* (656) |