THYROID CANCER

Payal D. Shah and Eric J. Sherman

Epidemiology

- Incidence: 240% ↑ in incidence over prior 3 decades, in part due to ↑ detection of small papillary CA; incidence of anaplastic thyroid CA declining
- Mortality: Mortality rate stable; accounts for 95% of endocrine CA but 66% of endocrine CA death
- Subtypes: 80–85% of malignant epithelial thyroid tumors in developed countries are papillary; 3–12% medullary; 1–3% anaplastic
- Median age at dx early 40s for papillary thyroid CA, late 40s for follicular; 60–70 y for anaplastic

Epidemiology

Risk Factors

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>• <strong>Radiation</strong> exposure to thyroid gland (esp younger age wil latency period at least 3–5 y, linear relationship to exposure dose, nuclear fallout events including Chernobyl)</td>
</tr>
<tr>
<td>Follicular</td>
<td>• Age</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>• Female sex</td>
</tr>
<tr>
<td></td>
<td>• FHx (4–10x ↑ risk in 1st degree family members of papillary/follicular CA pts)</td>
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<tr>
<td>Medullary</td>
<td>• FMTC syn including FMTC, MEN-2 (20–25%)</td>
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<td>• 75–80% sporadic/nonfamilial involving RET gene Mt</td>
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Biology

- **MAPK signaling pathway**: Mt involving one of three genes, RET/PTC (rearrangement in 20% of adult sporadic papillary carcinomas), BRAF, or RAS in 70% of papillary carcinomas; rarely overlap in same tumor
- **PAX8-PPAR** in 35% follicular carcinomas, some Hurthle cell

Clinical Presentation and Diagnosis

- **Commonly p/w incidental solitary thyroid nodules**: Median tumor size 2–3 cm; 5–10% malignant; higher percentage if radiation exposure; majority hypofunctional; presence of microcalcifications, irregular margins, spotty intranodular flow, hypervascularity are suggestive of malignancy
- **U/S**: For FNA, to assess number & characteristics of nodules
- **FNA**: Accuracy of dx 70–97%; varies w/sample quality, cytopathologist skill; ~70% benign, 4% malignant, 10% suspicious/indeterminate; 17% insufficient sample
- **Medullary**: Familial often detected by screening w/stimulation tests/molecular analysis; sporadic by asx thyroid mass; secretory diarrhea if bulky disease w/ high calcitonin
- **Anaplastic**: Prior or concurrent dx of well-differentiated thyroid CA or benign nodular thyroid disease; rapidly ↑ palpable neck mass (median tumor size 8–9 cm); invasion into airways & recurrent laryngeal nerve leads to obstructive sx, hemoptysis, dysphagia, hoarseness; 20–50% have distant mets at dx in lung > bone, liver
- **Familial tumors tend to be more aggressive than nonfamilial**

Natural History and Prognosis

- **Natural hx**: 2/3 pts w/papillary carcinomas have disease limited to thyroid at dx
- **Prognosis**: Papillary: 90–95% long-term survival; follicular: 70–80% long-term survival; distant mets strong negative prognostic indicator; prognosis ⇒ stage; anaplastic: Median survival 4–5 mos from dx
- **Poor prognostic factors for well-differentiated thyroid CA**: Age >45 y, male sex, poorly differentiated histology, tumor size, extrathyroid extension at dx; nodal involvement does not confer ↓ survival in younger pts
- **Mayo Clinic Model**: AGES (age, tumor grade, tumor extent, tumor size)
BRAF Mt: May be a/w ↑ likelihood of extrathyroidal extension, node met, recurrence; point Mt in 45% of thyroid papillary carcinomas (Cancer 2012;118:1764)

Staging
- **Papillary/follicular, under age 45**: Stage I: M0; Stage II: M1
- **Papillary/follicular, ≥45**: Stage I: T1 (<2 cm confined to thyroid); Stage II: T2 (>2 but <4 cm confined to thyroid); Stage III: T3 & early nodal involvement; Stage IV: All else including M1
- **Medullary**: Stage I: T1, node negative; Stage II: T2–T3, node negative; Stage III: T1–T3, early nodal involvement (N1a); Stage IV: All T4, N1b, M1 disease
- **Anaplastic**: Stage IV

Pathology
- **Cell Derivation**: Papillary, follicular, Hurthle cell, anaplastic arise from follicular cells that produce thyroid hormones; Tumors usu PAX8 & TTF1 positive

<table>
<thead>
<tr>
<th>Pathology</th>
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</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>Papillae; follicular variant has no papillary areas; enlarged, ovoid nuclei that frequently overlap; <strong>propensity to invade lymphatic spaces so high incidence of regional node involvement</strong>; microcarcinoma &lt;1 cm</td>
</tr>
<tr>
<td>Follicular</td>
<td>True follicular carcinoma rare (5–10% of nonendemic goiter area thyroid malignancies); unifocal, thickly encapsulated, <strong>invasion of capsule/vessels frequent</strong></td>
</tr>
<tr>
<td>Intermediately differentiated tumors</td>
<td>10–15% tumors w/in category of papillary &amp; follicular subtypes including tall cell, columnar cell &amp; diffuse sclerosing variants, insular carcinoma types of papillary; Hurthle cell (oncocytic, oxyphilic) carcinomas as type of follicular; <strong>more aggressive biology</strong></td>
</tr>
<tr>
<td>Medullary</td>
<td>Arises from calcitonin-producing parafollicular C cells, w/c are embryologically from neural crest</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>“Giant cell” variant; possibly a/w dedifferentiation of previously well-differentiated tumor; rapidly growing, invasive</td>
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Treatment
- **Surgery**: Mainstay of tx for all subtypes, but rarely possible w/anaplastic; complications of total thyroidectomy include recurrent laryngeal nerve injury & hypocalcemia 2/2 hypoparathyroidism
- **Differentiated thyroid CA**: Levothyroxine suppression of TSH as it is a potential growth factor for microscopic CA deposits, RAI administration to ablate any nl thyroid remnant
- **Met disease**: RAI, external-beam radiotherapy, & chemotherapy (doxorubicin + platinum) for met disease; **TKIs (eg, sorafenib) have activity in iodine-refractory disease** (J Clin Oncol 2008;26:4714) & are the preferred tx by guidelines
- **MTC**: Total thyroidectomy w/b/l central compartment node dissection & at least unilateral neck dissection; radiation & chemotherapy not considered effective; targeted therapies **vandetanib** (J Clin Oncol 2012;30:134) & **cabozantinib** (J Clin Oncol 2011;29:2660) approved for tx of met disease; treat local recurrences surgically; **screen** for germline RET gene Mt as total thyroidectomy is preventive in young, at-risk family members
- **Anaplastic thyroid CA**: May require urgent tracheostomy; if unresectable at dx, radiation-based Rx, often w/chemotherapy for sensitization; **RAI not useful**
- **Tumor markers for surveillance**: Thyroglobulin (highly sensitive & specific in the absence of all nl thyroid tissue) for differentiated CA; surveillance w/CEA & calcitonin for MTC
SELLAR TUMORS

Jane L. Meisel, Monica Girotra, Kevin C. De Braganca, and Thomas J. Kaley

Sellar Masses

- Presentation
  - Neuro sx: HA (expansion of sella), diplopia (oculomotor nerve compression), pituitary apoplexy (sudden hemorrhage into the mass), CSF rhinorrhea (inferior extension of mass), visual field deficits
  - Hormonal abnormalities (hyper- or hyposecretion; see below)
  - Incidental finding on MRI done for other reason ("incidentaloma")

- Causes
  - Pituitary adenomas = most common cause; ~85% of sellar masses
  - Also: Physiologic pituitary enlargement (pregnancy, 1° hypothyroidism, 1° hypogonadism); cyst, abscess or AV fistula of cavernous sinus; hypophysitis (lymphocytic most common kind, seen in postpartum or in anti-CTLA-4 tx of malignancies); benign tumors (craniopharyngioma, meningioma); 1° malignant tumors (germ cell, chordoma, 1° CNS lymphoma, sarcoma, pituitary carcinoma-rare); met disease (breast/lung 1° most common)
  - In a large registry of pituitary tumors (N = 4122), 84.6% were adenomas, 3.2% were craniopharyngioma, 1.8% were Rathke cysts, 1.8% were Crooke cells (w/o adenoma), ~1% were meningiomas, 0.6% were mets, & 0.5% were chordomas. Sellar tumors of all other types each occurred no more often <0.5% of the time (CNS lymphoma 0.02%, GCT 0.15% as described below) (Eur J Endocrinol 2007;156(2):203)

- Evaluation
  - Sellar MRI to better characterize the lesion
  - Evaluation of hypothalamic-pituitary hormonal function

Pituitary Adenoma

- Classification: By size & cell of origin
  - Size: <1 cm = microadenoma; >1 cm = macroadenoma
  - Cell type: Arise from any type of cell of the anterior pituitary; can lead to ↑ secretion of hormone(s) produced by that cell and/or ↓ secretion of other hormones due to compression of other cell types
    - Gonadotroph:Usu clinically nonfunctional
    - Corticotroph:Usu causes Cushing
    - Lactotroph: ↑ PRL → hypogonadism (δ/γ)
    - Thyrotroph: Can be clinically nonfunctional (secreting only α or TSH-β subunits, or can cause hyperthyroidism from ↑ secretion of intact TSH)
    - Somatotroph: ↑ GH → acromegaly
    - Lactotroph/somatotroph combinations also occur, leading to sx of both

- Evaluation
  - MRI: Best imaging procedure to evaluate sellar masses
  - Evaluation of hypothalamic-pituitary hormonal function:
    - Hormonal hypersecretion is caused only by pituitary adenomas & defines the sellar mass as such
    - Hormonal hyposecretion can be caused by any hypothalamic or pituitary lesion; does not help narrow the ddx (unless DI is found, as this indicates a lesion/↓ ADH release from hypothalamus or stalk)

- Tx
  - Gonadotroph/other clinically nonfunctioning adenomas: If large enough to cause neuro sx (visual field abnormalities, etc.), TSS is 1st line; if no neuro sx, can consider TSS if extrasellar extension present (ie, elevating optic chiasm) or monitor w/q6–12 mos exams/MRIs. Post-op monitoring is w/MRI; if residual tissue grows progressively, consider repeat surgery or XRT.
  - Corticotroph: Complete removal of tumor via transsphenoidal adenectomy or anterior pituitary resection is 1st line; repeat surgery or XRT for persistent/recurrent disease; medical Rx for persistent/recurrent disease or while waiting for RT effect (adrenal enzyme inhibitors- ketoconazole, metyrapone; somatostatin analog- pasireotide; cabergoline). B/l total adrenalectomy can be considered in pts not cured by pituitary surgery, RT, &/or medical Rx
• **Lactotroph:** Tx if existing/impending neuro sx due to size (ie, >1 cm), hypogonadism or other sx due to inc PRL; DA agonist (cabergoline, bromocriptine) is 1st line to ↓ tumor size & dec prl. Pts w/nil PRL & no adenoma on MR while on low-dose DA agonist for at least 2 y, suggest trial of stopping drug w/careful monitoring of PRL/MR. If drugs ineffective (ie, substantial tumor/macroadenoma remains or sx due to ↑ PRL persist after tx), consider TSS. In pts w/very large macroadenoma who have considerable residual tumor after TSS not amenable to further surgery, consider DA agonist tx and/or XRT.

• **Thyrotroph:** Transsphenoidal resection is 1st line & cures 1/3, improves 1/3, leads to no Δ in 1/3 → many need additional tx (DA agonist/octreotide). βB can ameliorate s/s of hyperthyroidism.

• **Somatotroph:** TSS unless not fully resectable/surgical risk is too high, then consider medical tx w/LA somatostatin analog (if no impending neuro sx). If surgery results in normalization of serum IGF-1, no further tx. If IGF-1 still high, treat w/ somatostatin analog. If ineffective, add cabergoline; if this is ineffective, stop cabergoline & give pegvisomant alone or w/somatostatin analog. If still not successful, XRT or repeat operation.

**Primary Malignant Tumors**

- **Intracranial GCTs**
  - Arise from the pineal/suprasellar region (pineal = 2× as common)
  -Usu occur in children & through the third decade of life (up to 40% in young adults; M > F (particularly in pineal region)
  - Intracranial GCTs make up ~0.5–3% of pediatric CNS tumors in USA (more frequent in Asian countries) (Oncologist 2008;13:690)
  - Sx: Pineal region- HA, nausea, vomiting, lethargy, diplopia, pyramidal tract signs, & ataxia (from ↑ ICP/hydrocephalus), paralysis of upward gaze; suprasellar – hypothalamic, DI
  - Intracranial GCTs = germinomas & NGGCTs; the latter includes embryonal carcinoma, endodermal sinus tumor/yolk sac tumor, choriocarcinoma, teratoma (immature & mature), mixed tumors consisting of a combination of these types
  - **Histology:** Germinomas = lg polygonal undifferentiated cells w/abundant cytoplasm arranged in nests separated by bands of connective tissue; NGGCTs = varies depending on cell types present
  - **W/u/eval:** CSF & serum levels of AFP & B-hCG, (elevated levels primarily seen in NGGCT; CSF AFP > 1000 correlated w/poor prognosis); eval of pituitary/ hypothalamic function, CSF cytology, MRI brain/spine for staging as 10–15% will have leptomeningeal spread at time of dx (Oncologist 2000;5:312), bx

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Tumor Type</th>
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<tbody>
<tr>
<td>Low Risk</td>
<td>-Pure germinoma</td>
</tr>
<tr>
<td></td>
<td>-Mature teratoma</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>-Immature teratoma</td>
</tr>
<tr>
<td></td>
<td>-Mixed NGGCTs w/elements of tumor types from multiple risk groups</td>
</tr>
<tr>
<td>High Risk</td>
<td>-Choriocarcinoma</td>
</tr>
<tr>
<td></td>
<td>-Yolk sac tumor</td>
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<tr>
<td></td>
<td>-Embryonal carcinoma (Mixed NGGCTs composed mainly of these three histologies)</td>
</tr>
</tbody>
</table>
• **Tx:** Localized pure germinoma: Whole-ventricle RT (21–24 Gy) w/boost to 1° tumor (total tumor dose 40–45 Gy) (Int J Radiat Oncol Biol Phys 2003;56:511); neoadj chemo w/bleomycin & etoposide w/either CIS (BEP) or carboplatin (BEJ) can be used followed by a reduced dose of radiation, but chemo alone is a/w an unacceptable rate of relapse (Pediatr Blood Cancer 2004;43:126). Note: Tx bifocal tumors (pineal & suprasellar components) as localized tumors if MRI spine & CSF cytology are negative (Int J Radiat Oncol Biol Phys 82(4):1341–1351). Disseminated germinoma (as identified by MRI and/or CSF cytology) or tumors that do not demonstrate PR to chemo: Craniospinal irradiation NGGCTs: CIS-based chemotherapy followed by resection of residual tumor & craniospinal RT (Neuropediatrics 2005;36(2):71). Mature teratoma: Surgical resection (these do not respond to chemo/RT).

• **Chordomas**
  - Rare (diagnosed in ~300 pts in USA annually), slow growing, locally aggressive neoplasms of bone that arise from embryonic remnants of the notochord; can arise in the clivus
  - **Common sx:** HA, visual impairment, & anterior pituitary hormonal deficiencies
  - **Histologic subtypes:** Conventional (most common, cartilaginous or other mesenchymal components absent), chondroid (chordomatous & chondromatous features; predilection for the sphenoeoccipital region of the skull base); sarcomatous transformation (2–8% of chordomas; the sarcomatous component is interspersed w/areas of conventional chordoma; poorer prognosis)
  - **IHC:** + CK; + EMA >80% of cases; other stains variable
  - **Tx:** Surgical resection followed by RT; proton beam RT is best if available given importance of minimizing damage to surrounding structures (Neurosurg Rev 2009;32(4):403).

• **Primary CNS Lymphoma** involving the pituitary
  - **Common sx:** HA & visual/oculomotor impairment and/or deficiencies of anterior pituitary hormones & ADH/DI
  - **W/u:** Contrast-enhanced MRI = sellar mass w/variable extrasellar extension
  - **Tx:** Remains controversial- some treat as a systemic lymphoma; some w/CNS lymphoma regimens; some w/a combination of both (see Primary CNS Lymphoma)

**Metastases to the Pituitary Gland**
- Mets to the hypothalamus & pituitary gland = ~1–2% of sellar masses
- Most common w/BC in women & lung CA in men but also occurs rarely in other CA (renal cell, hepatocellular, prostate, colon)
- **Presentation** (sx occur in ~7% of pts): DI (most common presenting sx, if sx are present), anterior pituitary dysfunction, visual field defects, retroorbital pain, ophthalmoplegia
- **Tx:** Often involves local Rx (surgery or XRT) for sx mets; systemic Rx is dictated by 1° tumor type
- **OS** very poor (between 6 & 22 mos) (Neurosurg Focus 2004;16:68)
PHEOCHROMOCYTOMA AND MEN

Jane L. Meisel and Monica Girotra

PHEOCHROMOCYTOMA/PARAGANGLIOMA

Diagnosis

- **Classic triad of sx**: (HA, diaphoresis, tachycardia); refractory or paroxysmal HTN/"spells"; other = palpitations, tremor, pallor, SOB
- Screen w/24 h-urinary fractionated metanephrines + catechols in lower-risk pts; plasma fract metanephrines in pts w/high pretest prob of disease; if screen nl, no further testing needed but if metanephres ↑↑ then CT AP or MRI; if neg scan but suspicion still ↑, consider MIBG, PET, octreotide scan
- Catecholamine-secreting tumors in adrenal = pheochromocytoma; extra-adrenal catechol-secreting tumors = paragangliomas
- Pts at ↑ risk for pheo (MEN2, VHL), previously surgically cured pheos or paragangliomas, screen w/plasma fract metanephs → if mildly ↑ normetanephrine, perform 24 h-urinary fract metanephs, catechols, & imaging.

Treatment

- **Surgery**: Pre-op medical tx → control HTN, prevent HTN crisis, volume expansion
  - Pre-op α-adrenergic blockade (phenoxybenzamine) 10–14 d pre-op to normalize BP/expand contracted blood volume, then low-dose β-blockade (propranolol) after adequate α-blockade (~2–3 d pre-op)
  - Never start βB first b/c unopposed α activity can further ↑ BP.
  - Start ↑ -Na diet on 2nd/3rd d of α-blockade to counteract catechol-induced volume contraction & orthostasis w/α-blockade (note: May be contraindicated in CHF/renal insuff); Ca channel blockers also can be used
  - Metyrosine (inhibits catechol synthesis) when other agents ineffective or contraindicated or w/prior marked tumor manipulation (ie, RFA of mets)
  - Sporadic adrenal pheo- entire gland should be removed; Familial pheo (ie, MEN2, VHL)- ↑ incidence of b/l disease. If b/l adrenalectomy planned, pt should receive stress dose steroids

- **Malignant pheo (10%)**: No difference from benign pheo histo or biochemically; mets or local invasion often only clue, necessitating long-term f/u for all
  - Tx of malignant pheo:
    - Resect w/intent to cure (entering capsule predisposes to recurrence)
    - External XRT or cryoablation in pts w/painful skeletal mets; tumor irradiation w/131I-MIBG may be helpful; RFA of hepatic or bone mets
    - Chemo w/cyclophosphamide, vincristine, & dacarbazine (CVD) if tumor aggressive or low QOL; early evidence suggests TKIs may be useful (J Clin Endocrinol Metab 2009;94(5):386).

MEN

- **MENs** = hereditary tumor syn w/distinct patterns of organ involvement
- Mt in **MEN1** gene → type 1 multiple endocrine neoplasia (MEN1), Mt in RET proto-oncogene → type 2 multiple endocrine neoplasia (MEN2)

**MEN1**

- MEN 1 = autosomal dominant predisposition to tumors of parathyroid, anterior pituitary, & enteropancreatic cells

Clinical Presentation

- **Multiple parathyroid adenomas** → 1° HPT is often 1st manifestation, w/least 100% penetrance by 40–50 y (J Clin Endocrinol Metab 2001;86:5658); most pts asx & picked up by ↑ Ca w/in approp ↑ serum PTH
- **Pituitary adenomas** → prolactinoma most common; other types occur (ie, somatotroph, corticotroph, co-secreting, nonfunctional pituitary tumors); larger & more aggressive than those in non-MEN pts
- **Pancreatic islet cell/GI tumors** (1/3 of pts) → Zollinger–Ellison most common; also insulinoma, somatostatinoma, glucagonoma, VIPoma, clinically nonfunctioning tumors
- **Other tumors** → Carcinoid; cutaneous, adrenal tumors; pheo, ependymoma
Diagnosis and Treatment

• **Dx:** Based on presence of 2 of 3 main MEN-associated tumor types (1 of 3 in family member of known MEN1 pt). DNA testing for MEN1 gene Mt is commercially available; screening of family members w/serum Ca (given high presence of 1° hyperpara) can also be considered

• **Tx:** Subtotal parathyroidectomy (removal of 3.5 glands or removal of all 4 w/auto transplantation of parathyroid tissue) if sx ↑ Ca, nephrolithiasis, evidence of bone disease (↓ bone density, fracture); pituitary adenomas should be treated in the same way as sporadic pituitary adenomas (see section on Pituitary Adenomas); PPIs for gastrinoma (if well controlled w/PPI, role for duodenal/pancreatic surgery to prevent met disease unclear); surgery for insulinoma (usu local excision of tumor in pancreas head + distal subtotal pancreatectomy); medical mgmt of hormonal hypersecretion

• **Monitoring** (in established MEN1 pts, known Mt carriers, & at-risk family members): Look for sx of MEN1-assoc tumors (nephrolithiasis, amenorrhea, galactorrhea, erectile dysfunction, peptic ulcers, diarrhea, sx of hypoglycemia); √ annual serum Ca to detect axsx hyperpara that might require surgery; addt'l surveillance w/further biochemical & imaging modalities can be considered

**MEN 2**

• Subclassified into MEN2A, MEN2B, & FMTC

**MEN 2A**
- Autosomal dominant
- MTC, pheo, 1° parathyroid hyperplasia
- In pts w/only 1–2 above features, DNA testing for RET Mt or MEN2A features in 1° relative is required for dx
- Penetrance of MTC nearly 100% but variability in other manifestations
- Regular evaluation for pheo & hyperpara is recommended

**MEN 2B**
- Autosomal dominant
- MTC (develops earlier & w/more aggressive phenotype than MEN2A pts), pheo, mucosal neuromas, intestinal ganglioneuromas, Marfanoid habitus; not 1° HPT

**FMTC**
- Strong predisposition to MTC but not other CA
- Hard to distinguish from MEN2A/2B in small families

• In contrast to MEN1, early dx by genetic screening of “at-risk” family members in MEN2 important → presence of specific RET Mt predicts age of onset, aggressiveness of MTC, & likelihood of other endocrine neoplasms

• In an MEN2 family, a sample from a known affected pt should be tested to determine specific RET Mt for that family. When *germline* RET Mt found, family members of unknown status should be definitively genotyped

• Timing of ppx thyroidectomy, initiation of screening for pheo & 1° hyperpara depends on specific DNA Mt in the RET proto-oncogene

**Initial mgmt of MTC in suspected MEN pts:**
- Eval for pheo prior to thyroidectomy & if found, remove pheo first
- **Limited local disease or limited local mets:** Total thyroidectomy + proph central neck dissection; if LNs seen in lateral neck + no/limited distant mets: Also do lateral neck dissection; in presence of adv local or distant disease, less aggressive neck surgery can be considered

**Postoperative monitoring** for recurrent MTC (Kloos RT, et al. Thyroid 2009;19:565)

<table>
<thead>
<tr>
<th>Undetectable post-op calcitonin</th>
<th>-check calcitonin/CEA q6–12 mos</th>
<th>-neck US 6–12 mos post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable Post-op calcitonin &lt;150 pg/mL</td>
<td>-neck US ± baseline CT/MRI</td>
<td></td>
</tr>
<tr>
<td>Post-op calcitonin &gt;150 pg/mL</td>
<td>-CT or MRI of CAP + bone scan or bone MRI (to look for mets)</td>
<td></td>
</tr>
</tbody>
</table>

• **Persistent/met MTC:** XRT to neck/upper mediastinum in pts w/extrathyroidal disease/nodal mets (if curative dissection impossible)

• **Systemic tx for progressive met disease:** Oral TKIs (vandetanib, cabozantinib have good phase III data to support their use in this setting) (J Clin Oncol 2012;30(2):134; J Clin Oncol 2012;30(suppl; abstr 5508); dacarbazine-based chemo if disease progresses despite multiple TKIs; immunotherapy & radiolabeled octreotide (investigational)
TUMORS OF THE ADRENAL CORTEX

Elizabeth Won, Diane Reidy-Lagunes, and Mabel Ryder

Epidemiology

- Adrenal “incidentalomas” are adrenal nodules identified on imaging that is done for other reasons. Prevalence is 4% in abdominal imaging. Most are benign nonfunctional adenomas.
- ACC are extremely rare (incidence 1 to 2 per million), bimodal age distribution; peak incidence in early children & age 40–50

Etiology and Genetics of ACC

- RF are not understood due to rarity of adrenal carcinomas
- Majority are sporadic. Can be a/w hereditary syn: Li–Fraumeni, Beckwith–Wiedemann, MEN 1. High incidence in Southern Brazilian children, distinct germline TP53 Mt identified (R337H)
  - Susceptibility genes: Sporadic tumors have been a/w Mt in TP53

Clinical Manifestation

- 60% ACC are hormone secreting & p/w signs & sx of hormone excess (see table). Cushing syn, virilization syn (or mixed) are most common in malignant ACC. Feminization & hyperaldosteronism is seen in <10% of malignant cases.
- Nonfunctional tumors p/w abdominal/back pain, early satiety, wt loss

<table>
<thead>
<tr>
<th>Hormone Secretion</th>
<th>Presentation</th>
<th>Functional Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (Cushing syn, also known as ACTH-independent Cushing)</td>
<td>Wt gain, proximal weakness, hirsutism, psychiatric disturbances, HTN, hypokalemia, edema, central obesity, purple striae, hyperglycemia</td>
<td>ACTH, cortisol levels → overnight dexamethasone suppression test w/AM cortisol testing OR × 3 midnight salivary cortisol OR 24-h urine cortisol w/ suppressed ACTH</td>
</tr>
<tr>
<td>Aldosterone-secreting tumor</td>
<td>HTN, hypokalemia, alkalosis</td>
<td>Screening test: Serum aldosterone: Renin ratio &gt;30 w/an aldosterone &gt;15 If screen is positive, need to do either salt, saline, or captopril suppression testing to confirm dx</td>
</tr>
<tr>
<td>Androgen-secreting tumor</td>
<td>Hirsutism, deepening of voice, oligo/amenorrhea (in women)</td>
<td>DHEAS, testosterone</td>
</tr>
<tr>
<td>Estrogen-secreting tumor</td>
<td>Gynecomastia &amp; testicular atrophy (in men)</td>
<td>Estradiol</td>
</tr>
</tbody>
</table>

Workup and Evaluation of Adrenal Nodule/Mass

- Is there a h/o prior malignancy? → Met adrenal masses are common in pts w/active 1° disease; it is typically not the 1st presentation of 1° CA elsewhere
- Morphologic evaluation: CT scan or MRI abdomen to determine size, heterogeneity, lipid content (MRI), Hounsfield units (HU), margin characteristics
- Imaging characteristics of adenomas vs. carcinomas
  Adenomas: Often <4 cm, Hu < 10 precontrast, >50% Hu washout 15 min post-IV contrast, signal drop off on MRI chemical shift (Radiology 2002;222:629).
  ACC: Size >4 cm (usu much larger), w/heterogenous, irregular margins, local invasion w/evidence of necrosis on CT
- Must r/o pheochromocytoma prior to bx or surgery! Sporadic pheochromocytomas can be found in adrenal cortex. Pheo typically have high Hu on CT (>30 s) & bright on T2 MRI. Exclude pheo w/fractionated plasma metanephrines and/or 24 h urine metanephrines.
Staging
• Stage I: Tumor ≤ 5 cm
• Stage II: Tumor > 5 cm, no extra-adrenal invasion
• Stage III: Any size w/local invasion or regional LN spread
• Stage IV: Invasion into adjacent organs or distant met

Management: Functional Adenomas
• Surgery: If unilateral adenoma → laparoscopic unilateral adrenalectomy
• Medical mgmt: If nonsurgical candidate or bilateral hormone production.
  Hyperaldosteronism: Control HTN, hypoK+ w/spironolactone or eplerenone.
  Cushing sy: Tx of choice adrenalectomy (rarely bilateral, then bilateral adrenalectomy)

Management: Localized Adrenal Carcinoma
• Surgery: Complete surgical resection is the only potentially curative tx for adrenal carcinoma. Open adrenalectomy w/lymphadenectomy should be performed at specialized referral center. Complete resection may require removal of adjacent structures (liver, kidney, pancreas, spleen). ↑ risk for local recurrence & peritoneal spread when done laparoscopically.
• Adjuvant chemotherapy: Adjuvant mitotane to be considered, esp in high-risk pts; improves DFS vs. observation alone in retrospective study (NEJM 2007;356:2372).
  Duration of adjuvant tx unknown.
• Adjuvant radiation: Controversial; consider external beam RT to tumor bed, esp if close margins or tumor spillage. Reduces local recurrence rate, no DFS, OS benefit. (German ACC registry, J Clin Endocrinol Metab 2006;91:4501)
• Surveillance: Imaging & hormone testing every 3–6 mos

Management: Metastatic Adrenal Carcinoma
• Clinical trials should be considered for all eligible pts
  • Low grade tumor: Consider resection of 1° tumor & mets if >90% removable, particularly if functional. ↓ tumor burden, sx
  • Met/unresectable:
    EDP (etoposide, doxorubicin, cisplatin) + mitotane: ↑ RR (23% vs. 9.2%), PFS (5 mos vs. 2.1 mos), but no OS benefit vs. streptozocin + mitotane.
    Significant tox 58% AEs (FIRM-ACT, NEJM 2012;366:2189).
    No standard optimal dose of mitotane; some institutions recommend target serum levels of 14–20 μg/mL if tolerated. Studies suggest therapeutic levels need to achieve benefit. Mitotane is adrenolytic – pts should be put on hydrocortisone Rx empirically to prevent the development of adrenal insufficiency; can also cause aldosterone deficiency.
    Other options: Streptozocin ± mitotane, Cisplatin±etoposide ± doxorubicine or mitotane (NCCN compendium listing)
    • Medical mgnt of Cushing syn 2° to unresectable, met ACC includes mitotane, ketoconazole, metyrapone, & mifepristone.

Prognosis
• Overall prognosis remains very poor. Stage, completeness of resection, pathologic grade are most important prognostic factors.

<table>
<thead>
<tr>
<th>MSKCC Poor Predictive Factors</th>
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<tbody>
<tr>
<td>(1) Stage; presence of distant met at presentation</td>
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<tr>
<td>(2) Venous, capsular, or adjacent organ invasion</td>
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<tr>
<td>(3) Presence of tumor necrosis</td>
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<td>(4) Mitotic figures &gt;5/50 HPF</td>
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<tr>
<td>(5) Presence of atypical mitoses</td>
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<tr>
<td>(6) Mdm-2 overexpression (staining of target gene of p53)</td>
</tr>
</tbody>
</table>

(JCO 2002;20:941)

Figure 18-1