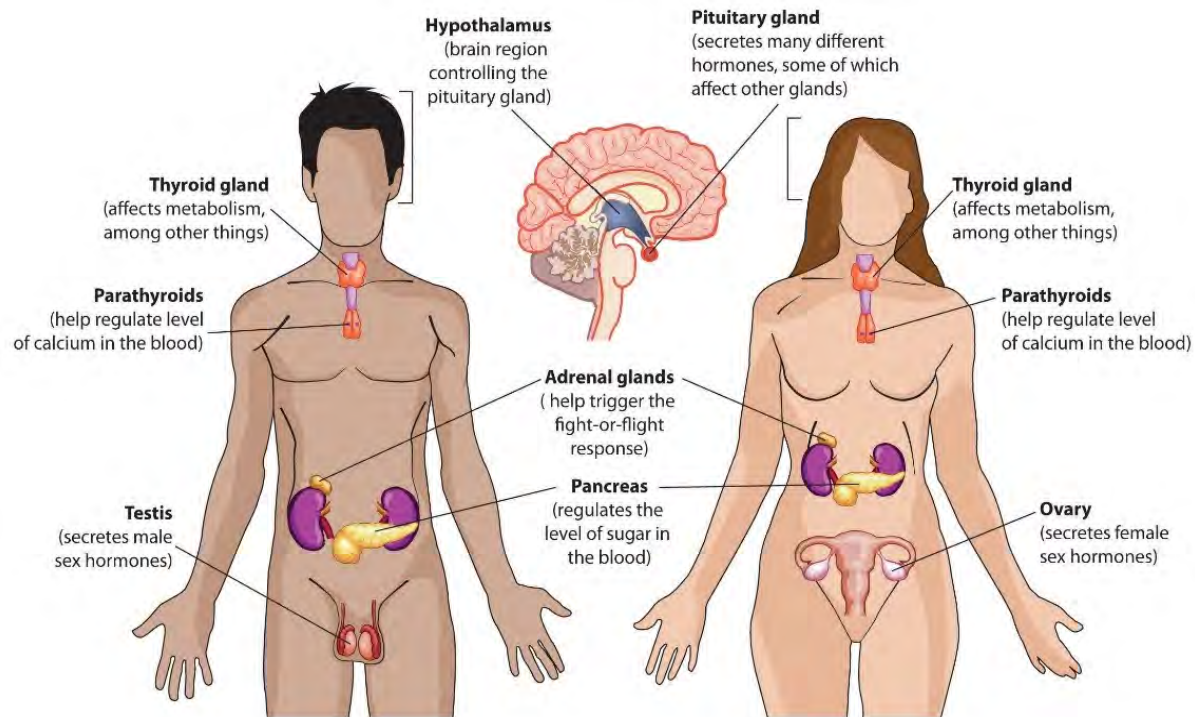


Endocrine Cancers

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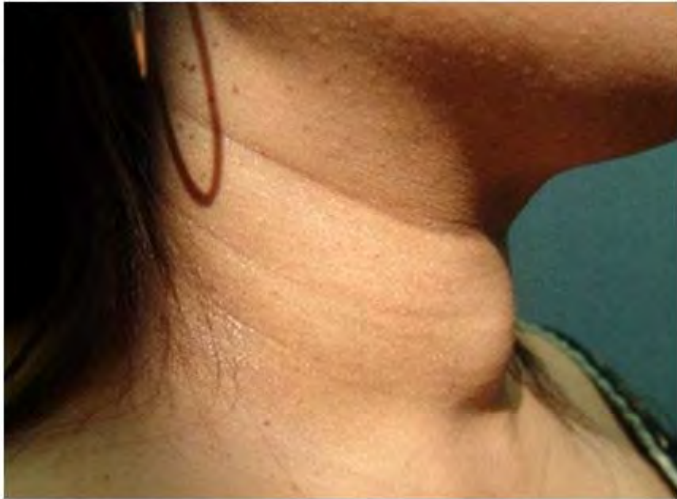
Cancer can occur in any of the endocrine glands



Thyroid cancer presents as a nodule in the thyroid gland



Thyroid Nodules



Types of Thyroid Cancer

- **Papillary (80%-85%)**: develops from thyroid follicle cells in 1 or both lobes; grows slowly but can spread
- **Follicular (5%-10%)**: common in countries with insufficient iodine consumption; lymph node metastases are uncommon
- **Medullary**: develops from C-cells, can spread quickly; sporadic .
- **Anaplastic**: develops from existing papillary or follicular cancers; aggressive, usually fatal
- **Lymphoma**: develops from lymphocytes; uncommon

Symptoms of thyroid cancer

- A lump, or nodule in the neck
- Enlargement of the neck
- Enlarged lymph nodes in the neck
- Hoarseness, difficulty speaking normally, voice changes
- Difficulty swallowing, or a choking feeling
- Difficulty breathing
- Pain in the neck or throat, including pain from the neck to the ears
- Sensitivity in the neck -- discomfort with neckties, turtlenecks, scarves, necklaces
- Persistent or chronic cough not due to allergies or illness
- Asymmetry in the thyroid (big nodule on one side, nothing on the other)

Papillary Carcinoma

- Arises from follicular cells of the thyroid gland.
- Most **common form of thyroid carcinoma** (almost **90%** of primary thyroid malignancies).
- Most commonly occur between **30 and 50 years of age (3rd to 5th decade of life)**.
- Some tumors associated with exposure to ionizing radiation.
- M:F ratio = 1:3

Papillary Carcinoma

Molecular pathology

- **RET-PTC rearrangements:** RET is proto-oncogene encoding membrane-bound **tyrosine kinase receptor** (RET is placed under control of genes constitutively expressed in thyroid follicular epithelium)
- Resulting activation of serine/threonine kinase pathway including Ras, B-raf, and mitogen-activated protein kinase (**MAP-K**) drives cellular proliferation
- Mutation of **B-RAF gene** present in up to 30-50% of papillary thyroid carcinoma. Point mutations lead to activation mimicking phosphorylated form of B-raf.
 - Can be with or without RET gene

Follicular Carcinoma

- The second most common form of thyroid cancer, accounting for 10% to 20% of all thyroid cancers.
- They tend to present in women, and at an older age than do papillary carcinomas, with a peak incidence in the forties and fifties.
- The incidence of follicular carcinoma is **increased in areas of dietary iodine deficiency,**

Follicular thyroid cancer

- 10-15% of all thyroid cancer cases
- Often difficult to distinguish from benign follicular neoplasms on FNA
- Lymph node spread is uncommon (8-13% of cases)
- Typical spread hematogenously with distant metastases (typically lung and bones) in 10-15% of cases
- Variant: Hurthle cell carcinoma
 - Higher rate of lymph node metastasis than classic FTC
 - Rarely presents with distant metastasis
 - However, highest incidence of late distance metastasis

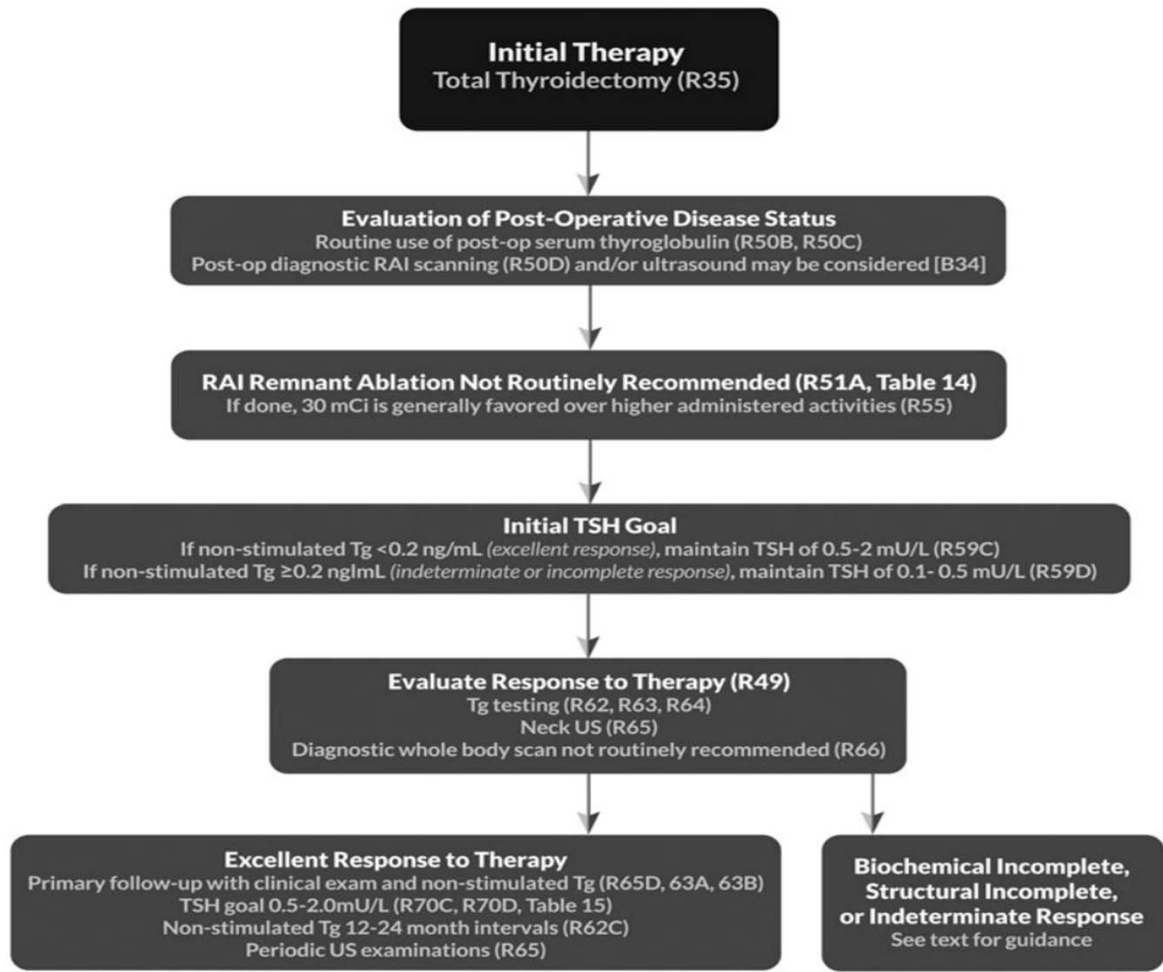


FIG. 5. Clinical decision-making and management recommendations in *ATA low-risk* DTC patients that have undergone total thyroidectomy. R, recommendation in text.

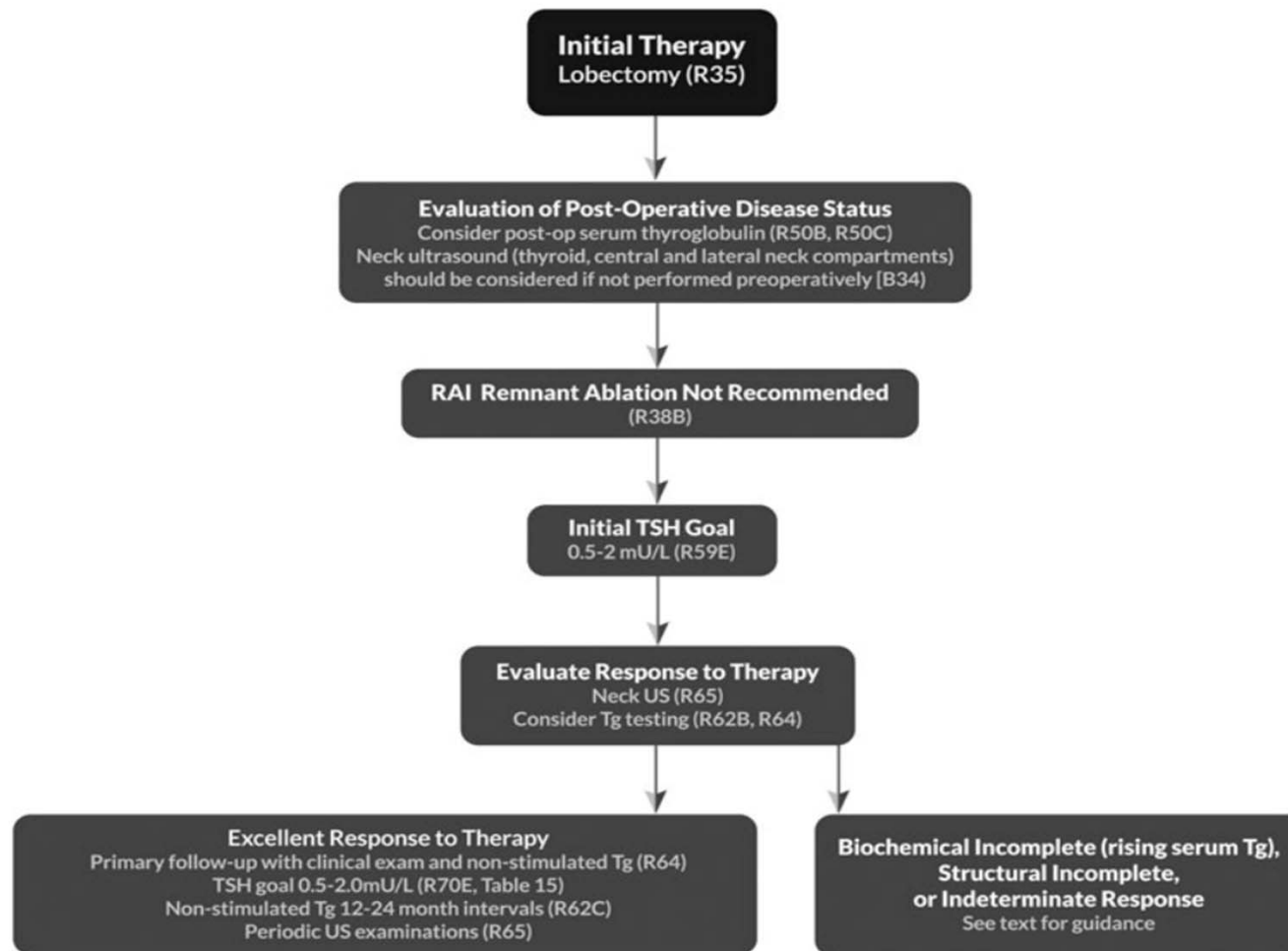
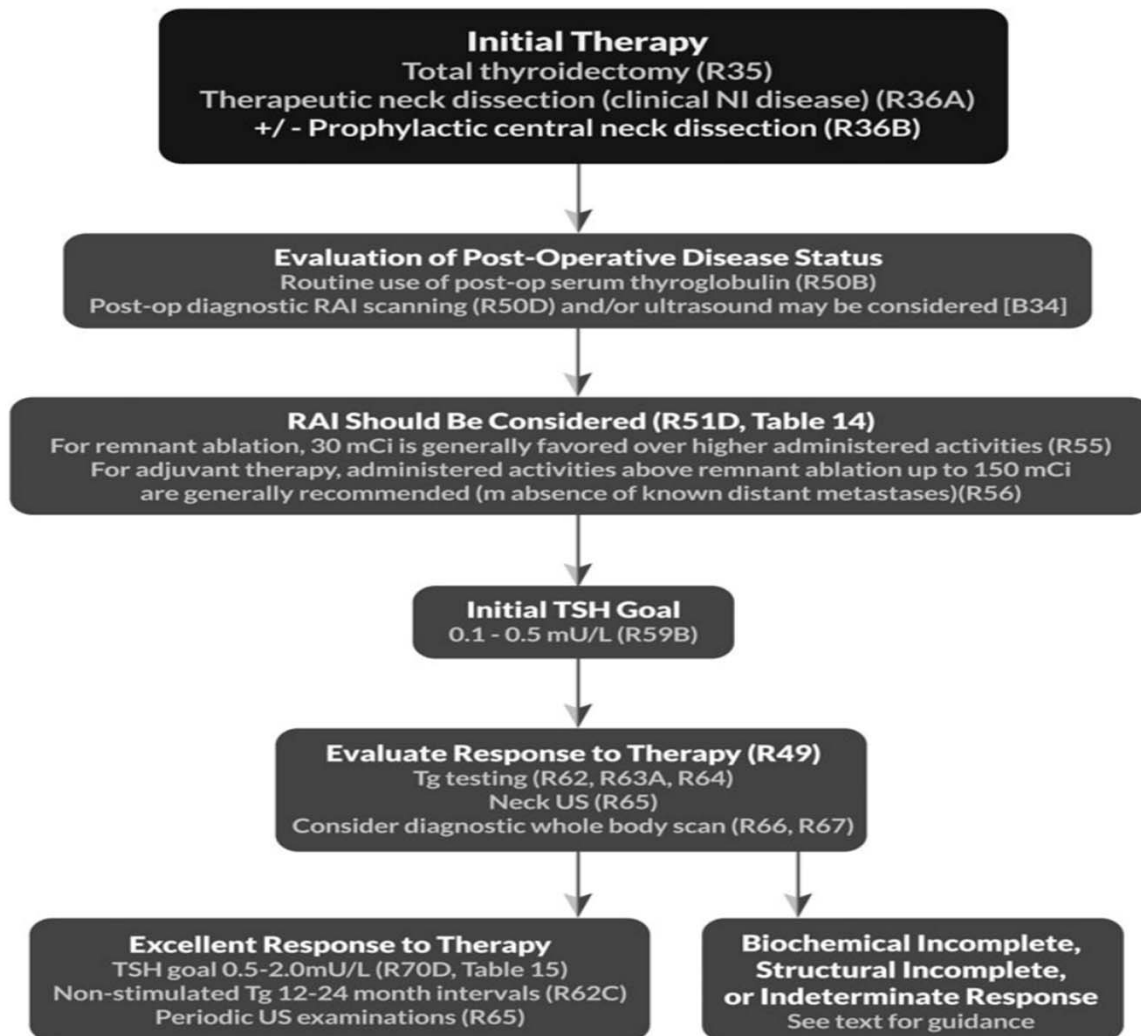


FIG. 6. Clinical decision-making and management recommendations in *ATA low risk* DTC patients that have undergone less than total thyroidectomy (lobectomy or lobectomy with isthmusectomy). R, recommendation in text.

FIG. 7. Clinical decision-making and management recommendations in ATA *intermediate risk* DTC patients that have undergone total thyroidectomy. R, recommendation in text.



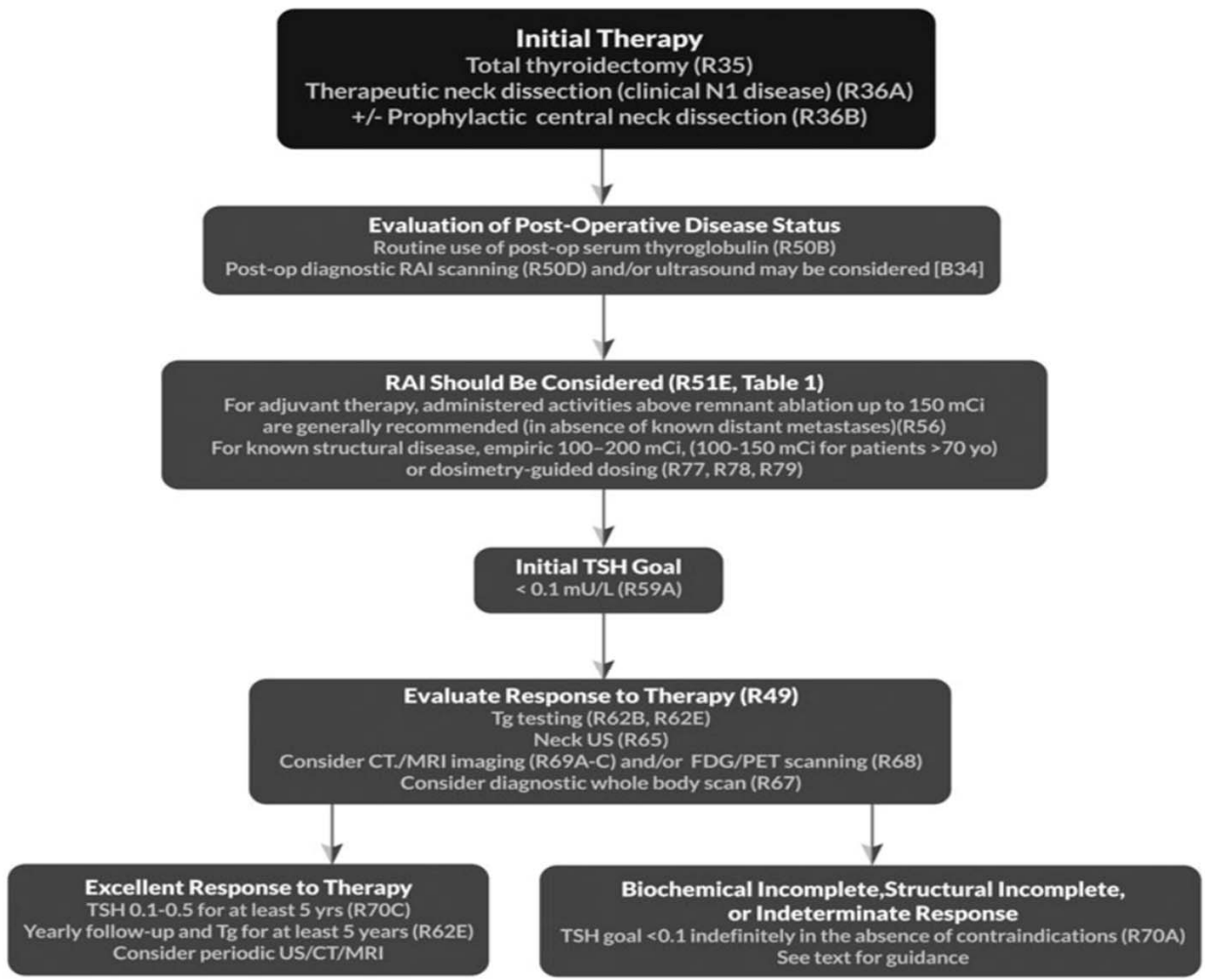


FIG. 8. Clinical decision-making and management recommendations in *ATA high risk* DTC patients that have undergone total thyroidectomy and have no gross residual disease remaining in the neck. R, recommendation in text.

Characteristics of Medullary Thyroid Cancer

- Occurs in 4 clinical settings and can be associated with other endocrine tumors
- More common in females than males (except for inherited cancers)
- Regional metastases (spread to neck lymph nodes) occurs early in the disease
- Spread to distant organs occurs late and can be to the:
 - Liver,
 - Bone
 - Brain
 - Adrenal medulla
- Usually originates in the upper central lobe of the thyroid

TABLE 3: Trials that led to FDA approval of vandetanib and cabozantinib for medullary thyroid cancer

Trial	Cabozantinib (Phase III)		Vandetanib (Phase III)	
	Cabozantinib	Placebo	Vandetanib	Placebo
Patients	n = 219	n = 111	n = 231	n = 100
Inclusion Criteria	Documented <u>progressive</u> disease		Locally advanced or metastatic disease	
Median PFS	11.2 months	4 months	NR (estimated 30 months)	16 months
Overall Survival	NR, 44% died at PFS cutoff (cross over not allowed)		15% died at PFS cutoff (patients allowed to cross over)	
Response Rate	28%	0%	44%	1%

FDA = US Food and Drug Administration; NR = not reached; PFS = progression-free survival.

ANAPLASTIC THYROID CANCER

- Uncommon type of cancer – annual incidence 1 to 2 per million persons – mean age at diagnosis 65 years
- Undifferentiated tumor of follicular epithelium
- Rapidly growing and extremely aggressive – disease specific mortality of almost 100%
- Very poor prognosis – initial management includes end of life issues and plan for comfort care measures; median survival 3 to 7 months
- Treatment options include surgery, external beam radiation and chemotherapy

TABLE 16. FACTORS TO REVIEW WHEN CONSIDERING KINASE INHIBITOR THERAPY^a

<i>Factors favoring kinase inhibitor therapy</i>	<i>Factors discouraging kinase inhibitor therapy</i>
<p>Imminently threatening disease progression expected to require intervention and/or to produce morbidity or mortality in <6 months (e.g., pulmonary lesions or lymphadenopathy likely to rapidly invade airways, produce dyspnea, or cause bronchial obstruction).</p> <p>Symptomatic disease (e.g., exertional dyspnea, painful unresectable adenopathy), not adequately addressable using directed therapy.</p> <p>Diffuse disease progression as opposed to focal progression (e.g., in multiple lung metastases, as opposed to a few growing lesions)</p>	<p>Comorbidity including</p> <ul style="list-style-type: none"> • Active or recent intestinal disease (e.g., diverticulitis, inflammatory bowel disease, recent bowel resection) • Liver disease • Recent bleeding (e.g., ulcer/GI bleed) or coagulopathy • Recent cardiovascular event(s) (e.g., CVA, MI) • Recent tracheal radiation therapy (this is associated with increased risks of aerodigestive fistula with kinase inhibitor therapy) • Cachexia/low weight/poor nutrition • Poorly controlled hypertension • Prolonged QTc interval/history of significant arrhythmia (includes ventricular and bradyarrhythmias) • Untreated brain metastases (controversial) • Recent suicidal ideation (suicide has been reported in depressed patients receiving TKIs) <p>Life expectancy based upon other comorbidities estimated to be too brief to justify systemic therapy</p>

^aBone metastases are often poorly responsive to kinase inhibitor therapy (see Bone-Directed Agents in section [C47]).
GI, gastrointestinal; CVA, cerebrovascular accident; MI, myocardial infarction; TKI, tyrosine kinase inhibitor.

TABLE 17. POTENTIAL TOXICITIES AND RECOMMENDED SCREENING OR MONITORING APPROACHES
IN PATIENTS STARTED ON KINASE INHIBITOR THERAPY

<i>Toxicity</i>	<i>Recommended screening/monitoring</i>
Hypertension	Frequent blood pressure monitoring, most critical during the first 8 weeks of therapy; if hypertension is induced, therapy should be individualized to patient response <ul style="list-style-type: none"> • <u>Note</u>: effective and expeditious management of hypertension is critical - and may reduce potential for cardiotoxicity. If antihypertensive therapy is needed, calcium channel blockers (e.g., amlodipine) may be most effective.
Cutaneous/mucocutaneous toxicities	Careful patient reporting of rash/mouth sores, patient awareness and education related to increased potential for photosensitization/sunburn.
Hepatotoxicity	Serial assessment of alanine serum transferase (AST), alkaline phosphatase and bilirubin - most critical during the first 8 weeks of therapy <ul style="list-style-type: none"> • <u>Note</u>: dose reduction of kinase inhibitor therapy is commonly required due to hepatic toxicity
Cardiotoxicity	ECG pretherapy and frequently during therapy <ul style="list-style-type: none"> • Hold (or do not initiate) kinase inhibitor therapy if QTc >480 ms Echocardiogram: elective, but recommended in any patient with cardiac history and especially important in patient with hypertension, symptoms consistent with congestive heart failure or coronary artery disease and in patients receiving sunitinib
Hypothyroidism	TSH should be assessed frequently, with levothyroxine dosage altered in response to rising TSH if observed
Nephrotoxicity	Serial serum creatinine, urine analysis with protein determination,
Hematological toxicities	Serial CBC/diff
Pancreatitis	Serial amylase
Teratogenicity	Pretherapy pregnancy testing and effective contraception in women and men of childbearing potential

CBC, complete blood count; ECG, electrocardiography.

Adrenal cortical carcinoma

- Rare, 0.5 and 2 per million
- Aggressive tumor, median survival of 15 months
- Over half show local invasion or metastases at the time of presentation
- Functioning tumors account for 24% and 74% of cases
- Cushing's syndrome, virilization
- Large tumors, 3 – 40 cm, 50 gm
- Uncapsulated, invasion into the capsule if present
- Cut surface, lobulations with fibrous bands and areas of necrosis and hemorrhage
- Invasion of major veins is a frequent finding, often leads to total occlusion, thrombosis, and embolism



Adrenal cortical carcinoma therapy

- Primary treatment is complete surgical open resection
- Need complete hormonal assessment prior to surgery
- Mitotane alone or in combination with other cytotoxic agents
- Palliative radiation therapy for locally advanced or distant mets

Pituitary carcinoma

- Pituitary carcinomas are rare. They present as a pituitary adenoma
- Malignancies that arise in the parasellar region include: germ cell tumors, sarcomas, chordomas and lymphoma
- Metastases to the hypothalamus and pituitary gland account for 1-2% of sellar masses – breast and lung cancer

PITUITARY GLAND

