

# **Therapeutic Approaches to Patients with Advanced Thyroid Cancer**

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## Clinical Approach

- Micro-dissect the clinical history
  - Review and verify the pathology
    - Slide review by expert pathologist
    - Immunohistochemistry if needed
  - Document each radiological exam
    - Iodinated contrast decreases radiiodide uptake
    - Delineate all sites of disease
  - Know all medical problems, medications, and co-morbid conditions

## Clinical Approach

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- Restage
  - CT scan, MRI, Ultrasound, Nuclear Scan (SESTAMIBI, 18FDG-PET, Thallium), Bone Xrays
  - No assumptions
    - Biopsy metastases if not sure
    - Evaluate inconsistencies

## Aggressive Thyroid Cancer: Histological Features

- Growth pattern
  - Solid, Trabecular, Scirrhous, Invasive, Size
- Histological Subtypes
  - Papillary
    - Tall cell, Columnar cell, Oxyphilic (Hürthle)
    - Typical with extrathyroidal invasion
  - Follicular
    - Oxyphilic (Hürthle)
    - Insular
  - Anaplastic

## Differentiation: Functional Features

- Iodine Uptake and Organification
- Thyroglobulin production
- Response to Thyrotropin
- Slow Growth (TSH-dependent)
- Low Distant Metastatic Potential

## Traditional Therapy

- Total thyroidectomy and node resection
- Radioiodine scanning and treatment
- Suppression of TSH with levothyroxine

## Progression of Papillary Carcinoma Dedifferentiation

- Loss of iodide concentration; thyroglobulin secretion persists
- Progression from micrometastatic to macrometastatic disease (local, lung)
- Increased rate of growth of metastases
- Diverse dissemination to distant sites (e.g. liver, pleura, brain, bones, etc.)
- Progression to critical tumor burden
- Death

## Genesis of Anaplastic Thyroid Carcinoma

- Usually found in association with papillary or follicular cancers
- Often a history of long-standing goiter
- Terminal dedifferentiation of pre-existing papillary or follicular cancer
  - Loss or mutation of p53 gene
  - Other Oncogenes
    - Ras
    - Nm23
    - C-myc

## Dealing with Aggressive Disease: Overview

- Make optimal use of standard therapy (exception: anaplastic carcinoma)
  - Suppression of TSH with levothyroxine
  - I-131 therapy (treatment & diagnostic use)
- Protect the thoracic outlet
  - Surgery
  - External beam radiotherapy
- Protect vital organs/sites
  - Brain, spine, pleural space
  - Enhance pulmonary capacity, treat infections
- Thalidomide, Paclitaxel
- Appropriate use of phase 1 or 2 clinical trials

## Effect of Dedifferentiation: Suppression of TSH

- TSH suppression correlates with outcome
- Changes with Dedifferentiation
  - Decreased number of TSH receptors
  - Possible defects in signal transduction
  - Despite changes, growth rate same or increased
    - Suggests importance of other growth factors
    - No way to distinguish which tumors have TSH-dependent growth
- Suggest: maintain suppression of TSH

## Augmentation of <sup>131</sup>I Effectiveness

- Uptake
  - TSH stimulation
  - Stable iodide depletion
- Iodide Retention
  - Lithium carbonate
  - Hypothyroidism
- Magnitude of Dose: limited only by toxicity
  - Dosimetry (200 REM red marrow limited)

## <sup>131</sup>I Scan negative, elevated Thyroglobulin

- No known macroscopic tumor sites: Administer therapeutic I-131 (>100 mCi)
  - Post-therapy whole body scan positive
    - Identifies tumor sites
    - May effect therapy
  - Post-therapy whole body scan negative
    - Look for thyroglobulin response
    - If no thyroglobulin response, defines lack of effective NIS activity &/or I<sup>-</sup> retention

## <sup>131</sup>I Scan negative, elevated Thyroglobulin

- Macroscopic disease evident on x-rays (may need to rule out second primary by biopsy)
  - Rule out stable iodide contamination
    - Contrast from CT scan interferes for 10-12 months
    - Verify that 24-hour urine iodide <50 µg on one week low iodine diet
  - No role for empiric I-131 therapy

## Management Goal: Find the tumor

- Defines therapeutic options
  - Localized metastases or recurrence
    - Surgical Resection &/or XRT
  - Disseminated disease
    - Palliative or experimental therapies
- Methods
  - Ultrasound, MRI, CAT scanning
  - Nuclear: <sup>201</sup>Tl, <sup>99m</sup>Tc (Sestamibi or tetrofosmin)
  - PET (<sup>18</sup>F-fluorodeoxyglucose)

## Resect Macrometastatic Disease

- Ischemic & hypoxic tumor masses
  - Radiation resistant
  - Chemotherapy resistant
  - Selection pressure for p53 mutation/loss
- Critical metastatic sites: prolongs survival
  - Intracranial (may use gamma-knife)
  - Spinal cord
  - Hemorrhagic

## Systemic Efforts

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- Thalidomide
  - Anecdotal partial responses in anaplastic
  - Nearly completed phase 2 clinical trial for functionally dedifferentiated, rapidly progressive papillary or follicular cancers
    - Interim report 11/02 (Chemotherapy Foundation, NYC) at 17 evaluable patients
    - 76% responded (mostly disease stabilization)
    - Durability around 6 months
    - Toxicity: sedation, neuropathy, constipation

## Systemic Efforts

2

- Paclitaxel (Taxol®)
  - Anaplastic Cancer: phase 2 clinical trial
    - >50% response rate
    - Durability: around 4-6 months
  - Poorly differentiated (non-Anaplastic) tumor
    - No published trials
    - Anecdotal: Some partial responses with uncertain durability

## External Beam Radiotherapy

- Purpose
  - Local control of tumor: critical sites
  - “Clean-up” after surgery
  - Debulk tumor prior to surgical resection
  - Palliation (bone mets, painful sites)
- Method
  - High dose, hyperfractionation
  - Chemoradiosensitization: unproven, higher morbidity
  - “Gamma Knife” useful for intracranial mets

## Future Potential Therapies

- Restore Radioiodide Response
  - Failure of retinoids
  - Likely mechanism: epigenetic inactivation (butyrate, depsipeptide)
- Inactivate Chemotherapy Resistance
  - MRP inhibitors
  - Additional mediators likely
- New Antineoplastic agents
- Other: Hypoxic cytotoxins, antiangiogenesis agents, p53 transfection