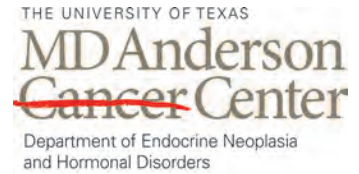




Differentiated Thyroid Carcinoma



Making Cancer History®

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Differentiated Thyroid Carcinoma

Thyroid cancer is the most common endocrine malignancy, affecting 450,000 people in the United States. Thyroid carcinoma is on the rise, with 44,670 new cases

estimated to occur this year. The median age of diagnosis is 45 years and children can also be affected, although less than 10% of patients are diagnosed before 20 years of age at MD Anderson. Women are affected twice as often as men, yet men are twice as likely to die of the disease.

Differentiated thyroid carcinoma, derived from follicular epithelial cells (papillary and follicular thyroid carcinoma), constitutes 95% of all thyroid cancers.

Papillary thyroid carcinoma comprises the majority (85%) of differentiated thyroid carcinomas in the United States. Overall survival rate for papillary thyroid carcinoma corrected for age and sex, is 98%. Follicular thyroid malignancies have a less favorable prognosis than papillary tumors, especially in patients with fixed/invasive lesions. The overall survival rate is 92%. Worse prognoses are associated with patients who are diagnosed at an older age and patients who present with metastatic disease.

Although there are many clinicopathologic staging systems for differentiated thyroid carcinoma, the AJCC staging system (TNM method) is the most useful for prediction of overall and disease-free survival and the one generally used in our institution.

Etiology of thyroid carcinoma is not clear in most cases, however, it appears that 10% of differentiated thyroid carcinoma patients have some radiation exposure to the head and neck region. For example, the external source of radiation from the Chernobyl nuclear accident led to a 3 to 75-fold increase in the incidence of papillary thyroid carcinoma in the fall-out regions. Less than 5% of differentiated thyroid carcinoma patients have a familial connection to the disease. Familial syndromes associated with differentiated thyroid carcinoma include Cowden Syndrome

(mutation in PTEN gene) and Gardner syndrome (familial adenomatous polyposis).

Differentiated thyroid carcinoma tumor mutations have been of increasing interest due to the development of targeted therapies for the treatment of metastatic disease. Mutations in the BRAF, RAS, or RET/PTC rearrangements are present in most differentiated thyroid cancers. While RET-PTC genetic alterations, commonly found in the Chernobyl radiation induced thyroid carcinomas, tend to have a better prognosis, BRAF mutations (papillary thyroid cancer) may behave more aggressively. Differentiated thyroid carcinomas also have a high dependence on angiogenesis. Similar to other tumors, epigenetic modifications of chromosomal DNA and histones, including the promoter gene of the sodium-iodine symporter, may also play an important role in promotion of tumor growth.

Initial Treatment

The treatment of differentiated thyroid carcinoma uses a three-pronged approach that includes surgery, radioactive iodine and suppression with thyroid hormone. External beam radiotherapy is occasionally needed in patients with extensive neck disease who are at high risk for recurrence.

Surgery

Adequate surgery is the most important treatment modality influencing outcomes and prognosis. Total thyroidectomy is the preferred initial surgical procedure for most patients (Continued on Page 2)

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with differentiated thyroid carcinomas >1cm at MD Anderson.

Microscopic regional nodal metastases are present in 80% of patients with papillary carcinoma. Only 35% of patients will have grossly detectable nodal (cervical or mediastinal) metastases. The presence of lymph node metastases increases risk for disease recurrence; however, unlike other malignancies, it is only a minor risk factor for mortality. Nodal metastases represent an uncommon finding in follicular carcinoma that may indicate decreased survival. Thus, when a patient presents with identifiable nodal disease, neck dissection should be performed to guard against recurrence. Preoperative ultrasound of the entire neck (not just the thyroid) is indicated to help identify the presence of nodal metastases and help the surgeon perform a more focused operation that will decrease recurrence and complication rates. This modality is routinely performed at MD Anderson. Calcium and phosphorus levels should be monitored postoperatively due to the distinct possibility of hypoparathyroidism caused by either vascular damage intraoperatively or inadvertent removal of blood vessels.

Radioactive Iodine Therapy

Iodine 131 (¹³¹I) has been advocated as adjuvant therapy for thyroid carcinoma. After ¹³¹I is preferentially taken up and trapped by the thyroid follicular cells and malignant counterparts, it begins to concentrate in the cells where beta rays are released. This activity causes high energy electrons to spew, inducing radiation cytotoxicity. Simultaneously, gamma rays are released, allowing the emission to be detected by a camera. Postoperative examination with radioiodine scanning, therefore, allows the residual regional or distant foci of disease to be identified and radioiodine can be used therapeutically to ablate such tumor deposits. Combined retrospective data suggests that radioiodine ablation reduces long-term, disease-specific mortality in the following patients: those with primary tumors 1cm in diameter or larger, those with multicentric disease, or those who present with evidence of soft-tissue invasion. More recent data has emerged that some low risk patients may not benefit from radioiodine, however.

Patients with known residual disease, be it nodal disease or distant metastatic disease postoperatively, have shown prolonged, progression-free survival with radioiodine treatment. Radioactive iodine (RAI) treatment is not recommended for solitary primary tumors < 1 cm in size unless high risk features or metastatic disease are present.

Uptake of iodine by follicular cells is stimulated by TSH and suppressed by increased iodine stores. For maximum uptake of radioiodine, thyroid hormone concentrations should be dropped sufficiently to allow the TSH rise to above >25 mU/L. This can be done by making withdrawals from the thyroid hormone or using recombinant

human TSH. Administration of "cold" (nonradioactive) iodine, such as that found in contrast material routinely used for computed tomography (CT) imaging and various invasive procedures, should be avoided for at least 2-3 months prior to a radioactive iodine scan. This "cold" iodine will interfere with the therapeutic radioactive iodine and may make the radioiodine scans falsely "negative." Urinary concentrations of iodine can be checked to assess a patient's total body iodine content prior to scanning and treatment with ¹³¹I. Using 2 - 5 mCi of either ¹²³I or ¹³¹I, a radioiodine scan for localization of uptake prior to ablation (pretreatment scan) is recommended and performed at our institution. An uptake of more than 5% on a whole-body scan indicates that excessive thyroid tissue remains and may warrant further surgical resection. If extensive locoregional disease is seen, additional surgery should be considered. Once the decision is made to treat the patient with radioactive iodine, an empiric dose is generally chosen for patients using these guidelines: 30-100 mCi for adjuvant ablation, approximately 150 mCi for nodal disease, and 200 mCi or more for metastatic disease outside the lungs. More strict dosing calculations using elaborate dosimetric techniques can be computed. Additionally, a post treatment scan is performed to assess for further uptake of radioactive iodine that was not previously seen on the pretreatment scan (i.e., regional or distant metastases).

Short-term complications, though rare, include radiation thyroiditis, neck edema, sialoadenitis, and tumor hemorrhage. These occur more often in the presence of bulky disease. Long-term complications, which increase with cumulative doses, include xerostomia, nasolacrimal duct obstructive, pulmonary fibrosis (if pulmonary metastasis is present and treated at high doses), and secondary malignant diseases, such as acute myelogenous leukemia. Some small studies have also suggested that patients treated with ¹³¹I may have a slightly higher risk for other secondary malignancies. A recent meta-analysis, however, found that the relative risk of any secondary primary malignancy was 1.19 (95% CI 1.04-1.36) relative to thyroid cancer survivors not treated with radioactive iodine; those treated with RAI had a 2.5 times greater risk of developing leukemia.

Thyroid Hormone Suppression Therapy

Patients are placed on thyroid hormone therapy after receiving radioactive ablation for: 1) correcting iatrogenic hypothyroidism and 2) minimizing potential TSH-stimulated growth of thyroid cancer cells. Enough thyroid hormone should be given to suppress TSH to 0.1-0.5 mU/L. In patients at higher risk of recurrence, TSH should be suppressed to less than 0.1 mU/L. Adverse effects of oversuppression of thyroid hormone include osteopenia, atrial fibrillation and possible cardiac hypertrophy.

External Beam Radiotherapy

External beam radiotherapy (EBRT) has a role in the treatment of papillary thyroid carcinoma.

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Upcoming Events

AACE 20th Annual Meeting and Clinical Congress. April 13-17, 2011. San Diego, CA. (www.aace.com)

Pediatric Endocrine Society 2011 Annual Meeting. April 30-May3, 2011. Denver, Colorado. (www.lwpes.org)

13th European Congress of Endocrinology's ECE 2011. April 30- May 4, 2011. Rotterdam, Netherlands (www.ece2011.com/)

Endocrine Society's Endo 2011, 93rd Annual Meeting & Expo. June 4-7, 2011. Boston, MA. (www.sherago.com/endocrine/AnnualMeeting.htm)

American Society of Clinical Oncologists (ASCO) 2011 Annual Meeting June 4-8, 2011. Chicago, IL. (www.asco.org/portal/site/ASCOv2)

American Society for Bone and Mineral Research (ASBMR) 2011 Annual Meeting Sept 16-20, 2011. San Deigo, CA. (<http://www.asbmr.org/Meetings/AnnualMeeting.aspx>)

4th Current Concepts in the Management of Thyroid and Parathyroid Neoplasms. Oct 20-23, 2011. Sante Fe, New Mexico. (website to be announced)

American Thyroid Association ATA's 81st Annual Meeting October 26-30, 2011. Indian Wells, CA. (http://www.thyroid.org/ann_mtg/2010_81st/index.html)

15th International Congress of Endocrinology. May 5-9, 2012. Florence, Italy.



(Busaidy, continued from page 2)

Although it is controversial, two retrospective studies have shown that it may be an effective adjuvant therapy to prevent locoregional recurrence in patients 45 years of age and older with locally invasive papillary carcinoma. Those who may benefit include patients with incomplete resection near the aerodigestive tract and/or those with extrathyroidal invasion and presumed microscopic residual disease. Patients younger than 45 years of age are generally not treated with EBRT, both because of their better prognosis and the possible late side effects of therapy including secondary malignancies.

Acute complications of external beam radiotherapy include esophagitis and tracheitis. Long-term complications include neck fibrosis, xerostomia, dental decay, osteoradionecrosis, and the risk of tracheal stenosis. Improved techniques to deliver radiation with fewer adverse events are being used in the treatment of cancer, including intensity-modulated radiation therapy (IMRT). A multidisciplinary approach is recommended and the patient should discuss the risk and benefits of EBRT with his/her surgeon, radiation oncologist and endocrinologist.

Follow Up

After the patient has had a total thyroidectomy followed by radioiodine ablation, the patient undergoes lifelong surveillance using both clinical and radiographic data. Follow-up includes an ultrasound of the neck and TSH and serum thyroglobulin if no distant metastatic disease is known or suspected. Thyroglobulin (Tg), a protein synthesized only by the thyroid follicular cells, is a good biomarker to assess the presence of residual, recurrent or metastatic disease. After total thyroidectomy and ablation, the Tg should be undetectable. A Tg measured in the same laboratory and in the context of TSH value has good sensitivity and specificity for noting recurrent disease. When the tumor has dedifferentiated and no longer secretes the Tg protein, Tg levels will be falsely low and cannot be relied upon.

If the Tg is undetectable at the follow-up visit, there should be continued clinical follow-up with imaging of TSH and Tg and periodic stimulated Tg. If, however, the Tg is elevated, a whole body diagnostic scan may be performed to evaluate for iodine avid disease. Other imaging techniques can be used in individual cases of thyroid cancer follow-up. These include a CT scan of the neck and chest, FDG-PET and MRI.

In 25% of thyroid cancer patients, Tg autoantibodies can falsely lower the reported Tg concentrations in immunometric assays as the antibodies interfere with the assay's ability to bind to Tg. The presence of antibodies after total thyroidectomy and postradioactive ablation may be indicative of the presence of cancer, although it can take years for thyroglobulin antibodies to disappear even in the absence of disease.

Recurrent Disease

The vast majority of differentiated thyroid carcinomas are curable and do not require further treatment after surgery and/or radioactive iodine. Approximately 15-20% of thyroid carcinomas re-

cur, and most of these recurrences are in the neck.

Surgery and Radioactive Iodine

Surgery in advanced thyroid carcinomas is most commonly used for recurrent neck metastases and metastasectomies in selected sites. Recurrences in the neck are most commonly seen in the thyroid bed or regional lymph nodes. Although most occur within the first five years after diagnosis, late recurrences do occur.

Surgery is considered the first line therapy in patients with gross nodal or recurrent neck disease and should include complete ipsilateral compartmental dissections of involved areas or modified neck dissections. This can be followed by further radioactive iodine (if the recurrent tumors took up radioiodine prior to surgery) and thyroid hormone suppression. One third to one half of patients may be free of disease in short-term follow-up. If the gross tumors do not take up radioactive iodine from previous post-treatment scans or preoperative radioiodine scans are negative, further postoperative radioactive iodine will be of limited benefit and may increase the side effects of further iodine therapy. External beam radiotherapy (as stated previously under "initial treatment") may be of benefit in select populations of patients with recurrent neck disease.

Metastatic Thyroid Carcinoma

Systemic therapy is the usual treatment of choice for progressive distant metastatic disease. The most common sites of metastasis are the lungs, bones, and other soft tissues in decreasing order. Although it is the most effective medical treatment for differentiated thyroid carcinoma, approximately 20-50% of all primary tumors and their metastases do not take up radioactive iodine. For those patients whose tumors are radioiodine avid, further treatment with radioactive iodine is warranted as it confers a better prognosis, especially in patients with negative radiological findings.

Dosimetric techniques may be most helpful in cases of distant metastases to determine the best dose.

Lack of RAI uptake by distant metastases confers a poorer prognosis. Most thyroglobulin positive patients with negative diagnostic scans have had other imaging modalities that showed evidence of disease. Repeat radioactive iodine therapies provide no survival advantage nor decrease in morbidity for these patients. Although controversial, a single dose of 100-150mCi of radioactive iodine therapy can be given to a patient with elevated thyroglobulin and a negative diagnostic scan. A post-treatment scan should be done and, if negative, further radioactive iodine should be avoided and use of systemic agents should be considered.

Because metastatic differentiated thyroid cancer can be stable and quiescent for many years, only patients with progressive or symptomatic disease should be treated with systemic treatments. Cytotoxic chemotherapies have been used in various combinations with response rates of 25-38%. Most of these are partial responses. Doxorubicin, cis- and carboplatin, epirubicin and taxol have all been used as single agent or in various combinations. Response rates appear to be short lived and with high toxicity.

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ENDOPERSPECTIVES® is a publication of the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas MD Anderson Cancer Center.

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(Busaidy, continued from page 3)

With the knowledge that many differentiated thyroid cancers have oncogenic mutations in the MAP kinase pathway, the dependence of these tumors on angiogenesis and the development of biologic agents that inhibit these pathways, tyrosine kinase and other anti-angiogenic inhibitors have been studied in various phase II trials. Although many of these agents have a partial response rate similar to cytotoxic chemotherapy, they have higher stable disease rates, more durable response rates and less toxicity.

Two small phase 2 trials evaluated sorafenib in differentiated thyroid carcinoma. Results showed a partial response rate around 20-27% and a large, developing stable disease rate (60%). Sorafenib is FDA approved for renal cancer and is, therefore, available for off-label use for patients that cannot enroll in a clinical trial. We recently reviewed our off-label experience with sorafenib and found similar response rates to the phase 2 trials. Progression-free survival was prolonged from 4 months pre-drug to 19 months after-drug treatment. A phase 3 randomized controlled clinical trial evaluating sorafenib versus placebo is currently underway at our institution and internationally. Pazopanib and sunitinib are both available for off-label use (FDA approved for renal cell carcinoma) and have also been studied in metastatic thyroid carcinoma. Most patients achieved stable disease, as well. Other agents that have been evaluated in clinical trials and appear promising include motesanib, axitinib, and lenalidomide. Despite these positive responses, most patients eventually develop other pathways of resistance as they progress through these agents. Future trials will need combination therapy to obtain synergism of the agents with minimal increased toxicity. These may include agents inhibiting the PI3 kinase pathway in addition to the MAP kinase pathway or a combination of cytotoxic chemotherapy with targeted agents.

In summary, for asymptomatic stable noniodine avid disease, thyroid hormone suppression and close observation is warranted. For progressive or symptomatic disease, consideration should be

given to putting a patient on clinical trial first. If the patient is not eligible for the clinical trial, off-label use of a tyrosine kinase inhibitor is advised. Cytotoxic chemotherapies should be reserved for patients that are deemed inappropriate or ineligible for these options.

Metastatic sites requiring special attention

Although most patients with metastatic disease will need systemic therapy, metastatic disease to certain sites deserves special attention. Surgical resection of brain metastases significantly improves median overall survival from 4 to 22 months in patients with one or more brain metastases. Current guidelines recommend resection when one CNS lesion is present. Radioiodine therapy and/or external beam radiotherapy should be considered after surgical resection with steroids to minimize tumor swelling. If CNS lesions are not surgically resectable, whole brain radiotherapy for numerous lesions or gamma knife radiosurgery to selected lesions should be used. Radioiodine should also be considered if the tumor concentrates iodine. If radioiodine is to be used, prior radiotherapy and concomitant steroids should be strongly considered to decrease tumor swelling.

Although bone lesions tend to concentrate radioiodine as well as lungs, complete resolution occurs less than 10% of the time. Metastases that cause pain or compression of the spinal cord or other vital organs necessitate treatment. Symptoms from painful bone lesions or spinal-cord-compressing lesions may be relieved by surgical treatment. External beam radiation therapy (EBRT), gamma knife radiosurgery and arterial embolization have also been used successfully to render bone lesions pain free. Intravenous bisphosphonates (pamidronate or zoledronic acid) are prescribed for painful bony metastases with some success as well. ¹³¹I treatment may follow surgical resection of distant metastatic disease if the tumor takes up radioactive iodine.

For a list of references, please email the editor at cstava@mdanderson.org.

Announcements

Please visit the Department of Endocrine Neoplasia and HD's exhibit at the upcoming AACE exhibition from April 13-17, 2011 at the San Diego Convention Center in San Diego, CA. Learn about our cutting edge patient care, research, innovative programs, and numerous specialties, united under one umbrella. We are also home to one of the largest clinical trial programs in the nation. You'll get to meet with physicians, researchers, and nurse practitioners who are Making Cancer History® everyday.

Introducing the New Bone Healthcare Program



The Bone Healthcare Program provides treatment for cancer patients with metabolic bone disorders or bone loss caused by cancer treatments. The Program helps streamline referral and triage processes for MD Anderson patients by bringing together consulting physicians from endocrinology, rheumatology and pediatric endocrinology. In addition to treatment, supportive care is provided by experts from radiology, pain management, rehabilitation and nutrition.

The Bone Healthcare Program provides evaluation and treatment of:

- * Osteoporosis
- * Low bone mass
- * Fractures
- * Height loss
- * Vitamin D deficiency

The Program offers increased availability of appointments and same-day consults, particularly for out-of-town patients. Additionally, the Program offers treatments at 3 convenient locations at MD Anderson Cancer Center in Houston, Texas. Patients are referred to the Program by their MD Anderson physician. Ask your doctor to contact the Internal Medicine Center at 713-563-7100, and ask to speak with a Bone Healthcare Program employee.

Recent News from the Endocrine Faculty Team

- A round of applause to Gilbert Cote, PhD, for being nominated for three awards in 2010: The Ben and Julie Rogers Award for Excellence, the Robert M. Chamberlain Distinguished Mentor, and the John F. McGovern Outstanding Teacher Award.

- The American Thyroid Association recently granted Steven Sherman, MD, the Outstanding Clinical Publication award in Thyroid for his article, Recurrence after Treatment of Micropapillary Thyroid Cancer. [Thyroid. 2009 Oct;19(10):1043-8]

- We would like to introduce Dr. Ferhat Deniz, who just joined the team as a postdoctoral fellow. He is a native of Turkey where he studied endocrinology and metabolism at the Gulhane Military Medical Academy in Ankara. He has written several publications on effects of hypogonadotropic hypogonadism in young men. He will be working closely with Dr. Sherman on the management of patients with advanced thyroid malignancies.

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New Clinical Trials

A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic RAI-Refractory Differentiated Thyroid Cancer (2009-0600)

This phase III study is focused on subjects with differentiated thyroid cancer (papillary, follicular, Hurthle cell carcinoma) who are refractory to radioactive iodine treatment. The objective of this study is to compare the treatment groups in terms of progression free survival evaluated by the Response Evaluation Criteria. For more information, please contact Madonna Pool, RN, at 713-792-9851.

A Phase I Drug-Drug Interaction Study of the Effects of XL 184 on the Pharmacokinetics of a Single Oral Dose of Rosiglitazone in Subjects with Solid Tumors (2010-0031)

The purpose of this study is to evaluate the effect of multiple daily doses of XL184 on single dose PK of rosiglitazone in patients with solid tumors (including DTC and RCC), and to evaluate the safety and tolerability of daily oral administration of XL184 and two single doses of rosiglitazone in subjects with solid tumors (including DTC and RCC). The study will also evaluate the plasma PK of XL184 after a single dose of rosiglitazone in patients with solid tumors, and assess the antitumor activity of XL184 in patients with solid tumors. For more information, please contact Pat Degen, Research Nurse Supervisor, at 713-792-2396.

A Phase II trial using RAD001 for patients with radioiodine refractory thyroid cancer (2010-0049)

The purpose of this study is to measure progression free survival in patients with progressive thyroid cancer and to measure objective response rate (complete and partial responses modified by RECIST criteria); provide symptom improvement in a cohort of patients with medullary thyroid cancer; and determine genetic expression of AKT, PTEN, P13K, and analysis of mutations such as B-raf on tumor tissue. For more information, please contact Pat Degen, Research Nurse Supervisor, at 713-792-2396.

A Single-arm, Multicenter, Proof-of-concept Study of Denosumab in the Treatment of Hypercalcemia of Malignancy in Subjects with Elevated Serum Calcium Despite Recent Treatment with IV Bisphosphonates (2009-0595)

This proof-of-concept study is designed to evaluate the potential for denosumab to treat hypercalcemia of malignancy that does not respond to recent treatment with intravenous bisphosphonates by lowering corrected serum calcium \leq 11.5 mg/dL (2.9 mmol/L) by study day 10. For more information, please contact Madonna Pool, RN, at 713-792-9851.

Treating Thyroid Cancer in a Research Setting



Gilbert J. Cote, PhD
Professor
Department of Endocrine Neoplasia and Hormonal Disorders

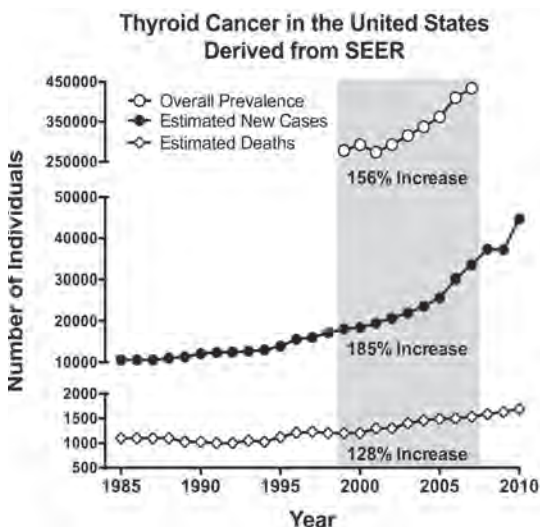
The Problem

Fortunately, 90% of the 450,000 individuals living with a diagnosis of thyroid cancer will not need to make significant changes in their lives. Most will only require synthetic thyroid hormone replacement and enhanced surveillance to

screen for possible recurrence. Despite this positive outcome, the larger picture is cause for concern. Thyroid cancer has more than doubled since 1990, (see Figure below) and among women, thyroid cancer ranked as the 5th most common newly diagnosed cancer in 2010. At least, the annual number of deaths has not increased at the same rate as incidence during these past 10 years, though this might merely reflect a lag, given the 5-year relative survival of 97.4% for the 1999-2006 review period. Regardless, an estimated 1,690 individuals will succumb to their cancer in 2010, and this number is expected to increase by approximately 1% annually. For these individuals, and for the larger patient population who live with the burdens of their cancer, there is currently no cure.

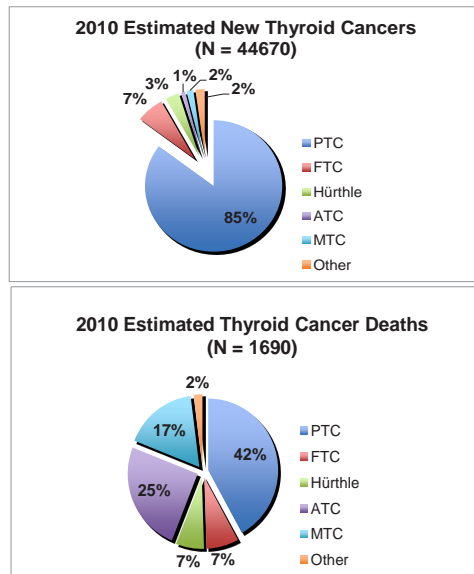
The Complex Nature of Deriving a Solution

There are two major considerations that need to be taken into account when developing treatments for thyroid cancer patients. First, when the cancer is caught in its earliest stages, and there is complete removal of the thyroid (thyroidectomy), the cancer is generally eliminated. Thus, prevention is the single most effective treatment for thyroid cancer. The



role of prevention has seen its way into clinical practice through the widespread use of ultrasound and image-guided biopsy, and in the case of hereditary thyroid cancer - prophylactic thyroidectomy based on genetic testing. The Thyroid Nodule Clinic and newly formed Multiple Endocrine Neoplasia Clinic at MD Anderson Cancer Center are specifically geared to offering a diagnosis at the earliest stages of thyroid cancer, yet, the presence of metastatic disease remains the single greatest cause leading to mortality, thus making it a primary target for new treatments. A second consideration is the heterogeneity of histology types found in patients dealing with the burden of living with thyroid cancer. The thyroid is comprised of multiple cell types with different functional characteristics; each with the potential to give rise to thyroid cancer. Broadly, follicular cells are the source of nonmedullary thyroid carcinoma and parafollicular cells (also called C cells) give rise to medullary thyroid carcinoma (MTC). Despite its anatomic location, MTC is actually a neuroendocrine tumor that is typically associated with aggressive growth. In patients with a palpable tumor the level of metastasis is thought to exceed 75%, which results in a disproportionate number of thyroid cancer deaths (see Figure on right). Nonmedullary tumors are significantly more prevalent, comprising ap-

proximately 95% of all thyroid cancers. Surprisingly, this frequency is similar to the percentage of follicular cells making up the thyroid, which may imply a common etiology. The primary cancers comprising this group are papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), Hürthle cell carcinoma, and anaplastic thyroid carcinoma (ATC). Despite their proposed similar cellular origin, the frequency and aggressiveness of these tumor types varies greatly (see Figure on right). For example, while PTC is by far the most common of these tumors, its mortality rate is an order of magnitude less than the undifferentiated ATC. Therefore, the process of deriving treatments for thyroid cancer lies in understanding what differentiates these tumors in their mechanisms of initiation, growth, and metastasis. For this reason a single treatment solution is unlikely.



Molecular Profiling of Thyroid Tumors

Advancements in the study of the human genome have developed a basic understanding of the role of genes in cancer initiation, maintenance, and metastasis. The discovery that activating mutations of the RET gene cause multiple endocrine neoplasia type 2, ushered in a new era of medullary thyroid cancer treatment. Ironically, just 3 years earlier this same gene, RET, was found to be somatically rearranged in PTC tumors to form an oncogene. Therefore, although thyroid tumors derive from two differing cell types they actually share a common molecular defect. We now know that genes involved in the RET tyrosine receptor kinase pathway (RET, RAS and BRAF) are common targets of aberrant activation upstream of MAPK signaling in thyroid cancer (see Table on Page 7). The molecular profiling of thyroid tumors, therefore, provides a basic identification of the primary genetic driver of tumor formation. In MTC that driver is mutant RET, while in PTC it has since been shown that activating mutations of BRAF drive tumor formation. The demonstration that a targeted tyrosine kinase inhibitor (TKI), Gleevec, could be used to successfully manage chronic myelogenous leukemia, dramatically changed how we treat cancer patients. With this finding, the ability to treat thyroid cancer patients through the pharmacological inhibition of RET became an attainable goal. Indeed, early in vitro studies by multiple groups suggested that Gleevec had some inhibitory action on mutant RET. In the absence of a selective RET inhibitor, thyroid cancer patients have been enrolled into clinical trials employing multi-kinase TKIs. At MD Anderson Cancer Center, alone, we have led more than 8 new thyroid cancer clinical trials and continue to take an active role in their development. These studies have developed a sense of both hope and intrigue. Drugs such motesanib, vandetanib, sunitinib, and sorafenib have yielded response rates higher than any previous cytotoxic chemotherapy in patients with (Continued on Page 7)

(Cote, continued from page 6)

metastatic disease. But these responses have been somewhat unpredictable, observed in only a fraction patients, and do not appear to correlate with the mutation status of tumors. Because studies have enrolled patients without knowledge of their tumor mutation status, the relevance of drug targeting to response remains largely unknown. Confounding the interpretation of responses is the fact that all of these molecules have potent antiangiogenic effects. The VEGFR inhibitor Axitinib demonstrates responses that show vascularization and microenvironment to be an important feature of a subgroup of metastatic thyroid cancers. Unfortunately, nonspecific antiangiogenic therapy is frequently associated with side effects including hypertension, fatigue, and diarrhea, and patients ultimately develop resistance to therapy. Looking forward there is a clear desire to minimize side effects while maximizing treatment benefit. The personalization of treatment through specific targeting of aberrant gene products uncovered in patient tumors is goal of the Endocrine Center. It is a goal that drives research to uncover new and more specific drugs, develop better analytical methods to define tumor-specific mutations, define the individual contributions of mutations to sustained tumor growth, and seek out the critical causes of tumor growth and recurrence. Through research at MD Anderson Cancer Center we are advancing our understanding in each of these areas.

Average prevalence of mutations in thyroid cancer

| Tumor Type | Prevalence (%) | Tumor Type | Prevalence (%) |
|-----------------------------|----------------|-----------------------------|----------------|
| <i>Papillary carcinoma</i> | | <i>Anaplastic carcinoma</i> | |
| BRAF | 45 | TP53 | 70 |
| RET/PTC | 20 | β-catenin (CTNNB1) | 65 |
| RAS | 10 | RAS | 55 |
| TRK | <5 | BRAF | 20 |
| <i>Follicular carcinoma</i> | | <i>Medullary carcinoma</i> | |
| RAS | 45 | PIK3CA | 20 |
| PAX8-PPAR | 35 | PTEN | >10 |
| PIK3CA | <10 | Familial forms RET | >95 |
| PTEN | <10 | Sporadic RET | 40 |

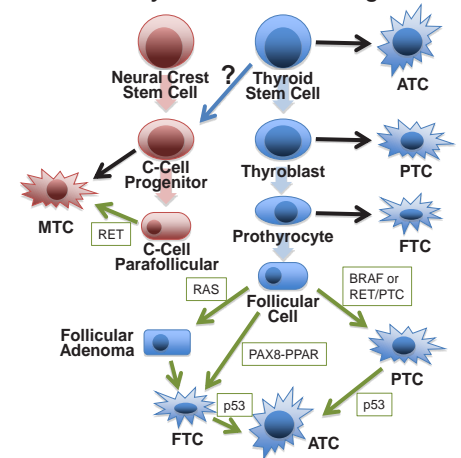
Adapted from Nikiforova et al. Expert Rev Mol Diagn 8: 83 (2008)

Cellular Origins of Thyroid Tumorigenesis

Though it may be straightforward to consider the two separate cellular origins of PTC (follicular cell) and MTC (C-cell), the spectrum of thyroid tumor behavior has led to a more thoughtful consideration of the origin of each tumor type. Two separate models show this diversity. The more widely accepted model is based on genetic profiling of tumors. In this model, tumor phenotype is driven by both an initiating mutation and subsequent driving mutations (see Figure on Page 8). The second model of thyroid tumorigenesis places a greater emphasis on the specific cell targeted by gene mutation. The model is based on recent growing evidence that many solid tumors contain a small subpopulation of cells capable of self-renewal and multi-lineage differentiation, termed “cancer stem cells”, “tumor initiating cells”, or “cancer propagating cells”. A major consideration of this model is that specific mutations occur in a thyroid progenitor cell, a cell type that, by definition, is capable of unlimited self-renewal and is driven to seek out an appropriate growth niche. While vagaries in defining the specific precursor origins of thyroid follicular and parafollicular cells remain, evidence is mounting for a “stem cell” model of thyroid cancer. One proposed model has undifferentiated ATC cancers deriving from mutation of the earliest thyroid progenitor stem cells and thyroid adenomas deriving from the most differentiated progenitors (see Figure). Our own work has identified the presence of cells with “stem-like” properties in MTC. These tumor cells can be visualized using specialized growth conditions and they express a different set of genes than those observed in the majority of MTC tumor cells. Cells with similar properties have recently been isolated from the tumors of patients with PTC, FTC, and ATC. Because these cells are resistant to standard chemotherapy and have been

proposed as the drivers of metastasis, they present a unique challenge to the development of specific cancer cures. Our group has been working to define molecular pathways that might serve as key therapeutic targets in cancer stem cells that could be used in combination with treatments that kill bulk tumor cells. Surprisingly, at least for MTC, the RET gene plays a critical role in stem cell function.

Models of Thyroid Cancer Tumorigenesis



Adapted from Al-Humadi et al. Cancer genomics proteomics 7:31 (2010)

Our hope is that through specific genetic profiling of tumor initiating cells (cancer stem cells) that we will uncover novel druggable targets.

Targeting Metastatic Thyroid Cancer

While distant metastases occur in less than 10% of patients with thyroid cancer, it represents the single greatest treatment challenge. Surgical approaches are typically untenable, radiation has proved largely ineffective, and pharmacologic approaches have only shown benefit since the introduction of targeted therapies. As previously mentioned, when targeted therapies have shown progress, the study design has typically not considered the genetic defects potentially driving tumorigenesis. When the genetic mutation of the tumor is considered, it is often as a result of germline testing demonstrating familial MTC (RET mutations), or somatic testing of the primary tumor performed in a research setting. As molecular typing of thyroid tumors becomes more prevalent there clearly will emerge a desire to personalize treatment strategies until an effective compound is found. However, it remains possible that even such a sophisticated course of action may be flawed. The factors driving thyroid cancer cells to metastasize remain largely unknown. As a result, it remains unclear if the genetic drivers of primary tumors are identical to those in metastatic tumors. Unfortunately, this is a difficult question to address given the general inaccessibility of these tumors. However, we do know that where these tumor cells may be accessible is in the blood stream – the primary pathway through which these cells travel to distant metastatic sites. Indeed, for breast, prostate and colon cancer the identification of “circulating tumor cells” strongly correlates with cancer prognosis. While a similar correlation remains to be made for thyroid cancer we have, at least, demonstrated the existence of circulating tumor cells in patients with MTC. We believe that these cells may more accurately reflect the molecular drivers of metastatic growth than the primary tumors, and provide the best opportunity for targeting therapy. Addressing this specific question is an active area of study within the department.

The Future of Thyroid Cancer - Refining Treatment Target Approaches

For the first time in recent history, thyroid cancer trials are realizing clinical benefit in patients with metastatic cancer. This offers new hope to patients, physicians, and researchers. But without a cure there remains a great need for continued clinical, translational, and basic research. The greatest successes remain in prevention. The need, moving forward, is to better understand the underlying causes of thyroid cancer metastasis and regulators of its growth. Molecular profiling has uncovered potential therapeutic targets. Clinical trials have demonstrated selective sensitivity to antiangiogenic therapy. And an ever-growing wealth of basic research involving cellular and animal models continue to define new pathways with critical roles in thyroid cell tumorigenesis. Our challenge is to sort through the plethora of findings and move forward with finite resources.

For a list of references, please email the editor at: cstava@mdanderson.org.

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