



Papillary Thyroid Carcinoma: Novel Treatment Approaches

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER



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Systemic chemotherapies for advanced, metastatic differentiated (papillary or follicular) thyroid carcinomas (DTC) have had limited effectiveness, with response rates typically 25% or less. Treatment with cytotoxic chemotherapy (such as doxorubicin, cisplatin, and taxanes) has been generally limited to patients with symptomatic or rapidly progressive metastatic disease unresponsive to or unsuitable for surgery, radioiodine, and external beam radiotherapy.

Recent biological discoveries have triggered a plethora of trials testing novel therapies for papillary thyroid carcinoma (PTC). Of prime importance has been recognition of key oncogenic mutations that activate signaling through the mitogen-activated protein kinase (MAPK) pathway, regulating growth and function in many cells. Numerous lines of evidence suggest that most PTCs arise from a single activating somatic mutation in one of three genes that code for kinases signaling upstream in the MAPK pathway: BRAF, RAS, and unique translocations producing RET/PTC oncogenes. Consistent with the "oncogene addiction" hypothesis, inhibition of these etiologic activating mutations could potentially lead to either tumor stabilization or regression, and therefore, interest arose in the therapeutic potential of inhibitors of these kinases.

A second development was recognition that angiogenesis plays a critical role in thyroid tumor cell growth and metastasis. Of the identified pro-angiogenic factors, vascular endothelial growth factor (VEGF) is critically important, mediated through binding to 2 receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR) that also trigger MAPK signaling. Small molecule inhibitors targeting signaling

kinases have been of keen interest for thyroid carcinomas, given the oncogenic roles of mutant BRAF, RET, and RAS, and the contributory roles of growth factor receptors such as VEGFR. These drugs are generally partially selective, inhibiting multiple kinases at nanomolar concentrations and often affecting multiple signaling pathways. Orally administered, these agents have tolerable common side effects that include hypertension, diarrhea, skin lesions, and fatigue. Interest in use of thalidomide arose following reported responses in individual patients with anaplastic thyroid carcinoma. Identification of abnormalities of nuclear gene regulation that affect differentiated function stimulated interest in targeting DNA methylation, histone deacetylation, and nuclear receptors as means to reverse these de-differentiating steps. The routes leading to drugs being tested for thyroid cancer in clinical trials have ranged from hypothesis-driven protocols as extensions of in vitro studies identifying a rationale for a particular drug's use, to empiric observations in phase I trials that certain therapies yielded clinical benefit in participating patients with thyroid cancers. Once clinical trials became available, awareness among patients grew rapidly. The remainder of this review will focus on findings from key studies that reflect this new paradigm for treatment.

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Motesanib

Motesanib (AMG 706; Amgen Inc.) is an oral, tyrosine kinase inhibitor (TKI) targeting VEGF receptors. In a phase I study performed in part at the M.D. Anderson Cancer Center, motesanib demonstrated antitumor activity in patients with advanced solid malignancies, including five patients with DTC. Based on this phase I experience, M.D. Anderson endocrinologists led an international, multicenter, phase II trial, testing the efficacy of motesanib therapy in patients with progressive DTC (1). The eligibility criterion of progression was based upon serial radiographic imaging studies within the preceding 6 months. Of 93 DTC patients who initiated therapy, one-third were still on drug after 48 weeks. Partial response was confirmed by subsequent imaging and independent radiologic review in 14% of the DTC patients, and another 35% of these previously progressive disease patients maintained stable disease for at least 24 weeks. The median progression-free survival was 40 weeks. Although the drug does not inhibit BRAF, patients with BRAF mutation-bearing tumors were less likely to progress while on drug, which may relate to higher dependence upon VEGF-mediated angiogenesis in such tumors. Overall, the drug was well tolerated, with side effects including fatigue, nausea, diarrhea, and hypertension. An unanticipated side effect of motesanib diphosphate therapy was a 30% increase in the mean dosages of levothyroxine required to maintain TSH suppression and 60-70% of patients experienced peak TSH concentrations out of the therapeutic ranges. Although Amgen decided not to pursue further studies of motesanib in thyroid carcinoma, this study was an important proof of concept, demonstrating the usefulness of a well tolerated angiogenesis inhibitor to halt progression of this disease.

Axitinib

Axitinib (AG-013736; Pfizer) is an oral TKI that potently blocks VEGF receptors. In a phase I study of 36 patients with advanced solid malignancies, one of five thyroid cancer patients experienced some tumor shrinkage. A multicenter phase II study that included M.D. Anderson investigators examined the efficacy of axitinib in advanced or metastatic thyroid carcinoma, starting at a dose of 5 mg twice daily (2). Of the 60 patients who started therapy, 50% had PTC, 25% had FTC (including Hurthle cell variants), and the remainder had either medullary or anaplastic carcinoma. Although response assessment was not possible in 25% of the patients, partial response rate was 31% in DTC, and median progression-free survival was 18 months. Common adverse events included

fatigue, stomatitis, proteinuria, diarrhea, hypertension, and nausea. Currently recruiting patients is a multicenter phase II study to determine the efficacy of axitinib in patients with metastatic DTC refractory to doxorubicin, or for whom doxorubicin therapy is contraindicated.

Sorafenib

Sorafenib (BAY 43-9006; Bayer Pharmaceuticals Corporation) is an oral, small molecule TKI targeting VEGFR-2 and -3, RET (including most mutant forms that have been examined), and the serine kinase BRAF. In preclinical studies, sorafenib prevented the growth of a cell line derived from a papillary thyroid cancer that contains the oncogenic RET/PTC1 mutation. In four phase I trials of varying doses and administration schedules of sorafenib in patients with solid tumors, the optimal therapeutic dose was found to be 400 mg twice daily. The most common or significant toxicities included hand-foot syndrome, rash, fatigue, diarrhea and hypertension.

Although no thyroid cancer patients were reported in these phase I trials, tumor shrinkage was reported in one thyroid cancer patient included in a large randomized discontinuation phase II trial for advanced solid tumors. Subsequently, two phase II trials were performed specifically in patients with metastatic PTC. Sponsored by the National Cancer Institute, one phase II trial recruited 58 patients in a 10 month period. Of 36 evaluable patients, confirmed partial response was seen in 8%, and minor response (defined as 23-29% reduction in tumor diameters) was described in another 19%. In the other phase II study, partial responses were reported in 23% of 30 patients, and another 53% had stable disease for at least 16 weeks.

Sorafenib is approved by the U.S. Food and Drug Administration as treatment for advanced renal cell carcinoma and unresectable hepatocellular carcinoma. Although not specifically approved for thyroid carcinomas, our thyroid cancer specialists are recommending off-label use of sorafenib in selected patients with progressive metastatic PTC for whom clinical trials are not appropriate. Our collective experience with sorafenib treatment will be presented at an upcoming national meeting by Drs. Maria Cabanillas and Naifa Busaidy. In a case report presented at recent annual meeting of the Pediatric Academic Societies, Dr. Steven Waguespack described a child successfully treated with sorafenib for lung metastases from PTC that had been progressing despite radioiodine therapy (3). As with any new medication, further experience with the drug is leading to identification of less common but significant toxicities, which

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Upcoming Events

11th European Congress of Endocrinology
April 25-29, 2009.
Istanbul, Turkey
(<http://www.ece2009.com/>)

AACE 18th Annual Meeting and Clinical Congress
May 13-17, 2009. Houston, TX. (www.aace.com)

The Endocrine Society
ENDO 2009, June 10-13, 2009. Washington, DC.
(www.endo-society.org)

World Congress on Thyroid Cancer, August 6-10, 2009. Toronto, Canada. (<http://www.thyroid2009.ca/>)

North American Neuro-Endocrine Tumor Society Annual Conference
Diagnosis & Management Strategies: A Multidisciplinary Approach
October 2-3, 2009
Charlotte Marriott City - Charlotte, North Carolina
(Additional information to be announced later)

ThyCa's 12th International Thyroid Cancer Survivor's Conference,
Oct. 16,18, 2009. Boston, MA. (<http://www.thyca.org/ConfFlyer2009.pdf>)

Third Annual Thyroid Neoplasms Conference, Oct. 21-24, 2009
El Dorado Hotel, Sante Fe, NM
(Additional information to be announced later)



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for sorafenib includes keratoacanthomas and other malignant cutaneous squamous cell lesions (4). Thus, only physicians familiar with management of adverse events of such therapies should consider their use in thyroid cancer patients.

Sunitinib

Sunitinib (SU11248; Pfizer) is an oral, small molecule TKI of all three VEGF receptors, RET, and RET/PTC subtypes 1 and 3. Prolonged partial responses have been described in DTC patients treated with sunitinib, 50 mg daily for 28 days followed by 14 days of no treatment per cycle. A phase II study is ongoing in patients with progressive DTC using this starting treatment regimen. Preliminary results report partial response in 13% of 31 DTC patients, and disease stabilization in another 68%. Common or severe adverse events include fatigue, diarrhea, palmar-plantar erythrodysesthesia, neutropenia, and hypertension. Like sorafenib, sunitinib is approved for treatment of renal cell carcinoma, and is therefore available for use in selected thyroid cancer patients with metastatic disease warranting therapy outside of clinical trials.

Gefitinib

Gefitinib (ZD1839; AstraZeneca) is an oral, small molecule inhibitor of the EGF receptor that was initially introduced for therapy of non-small cell lung carcinoma. Because many PTCs display activated EGFR signaling, and inhibitors have had demonstrated efficacy in pre-clinical models, a phase II study was initiated, examining the effectiveness of gefitinib in a mixed cohort of thyroid cancer. However, there were no complete or partial responses in the 25 evaluable patients.

Thalidomide/Lenalidomide

Thalidomide was found to be an angiogenesis inhibitor decades after it achieved notoriety as a teratogenic cause of neonatal dysmelia. However, the exact mechanism by which thalidomide exerts its antiangiogenic effects remains unknown. Based on a report of a patient with anaplastic carcinoma whose disease stabilized for 6 months on thalidomide treatment, a phase II trial was initiated to examine the efficacy of thalidomide in patients with progressive, metastatic thyroid carcinoma. Starting at 200 mg daily, the dose of drug was progressively increased as tolerated, with a median maximum daily dose of about 600 mg. Of 28 evaluable patients, 18% achieved a partial response, but toxicities were dose limiting in the majority of patients, including somnolence, peripheral neuropathy, constipation, dizziness, and infection. Given the suggested efficacy but high rate of adverse events with thalidomide, a subsequent phase II study was initiated using the derivative compound lenalidomide. A preliminary report de-

scribed 2 partial responses among 10 patients, but a full report of the study has not yet been presented.

Intranuclear targeting

The possible role of retinoid receptors to regulate iodine uptake by thyroid follicular cells was suggested by studies demonstrating that incubation of poorly differentiated thyroid cancer cells with 13 cis-retinoic acid could partially restore radioiodine uptake. Subsequent clinical trials yielded conflicting results. Recently, a synthetic agonist of the retinoid X receptor (RXR), bexarotene, was tested in a phase II trial in patients with radioiodine-unresponsive metastatic disease. After 6 weeks of therapy with bexarotene, 300 mg daily, radioiodine uptake was partially restored in 8 of 11 patients, but a clinical response with measurable tumor reduction was lacking. A similar rationale was the basis of studies of the histone deacetylase inhibitor depsipeptide. In a phase II trial in patients with radioiodine-unresponsive metastatic DTC, one of 14 patients exhibited dramatic restoration of uptake permitting therapeutic radioiodine administration. Significant cardiac toxicities were seen, however, including sudden death in one patient. The PPAR gamma agonist rosiglitazone was evaluated for the potential of restoring radioiodine uptake in 10 patients with unresectable metastases. In four patients, radioiodine uptake was visualized following eight weeks of therapy with oral doses up to 8 mg daily, but clinical response was limited. The lack of major clinical effect of restoring radioiodine uptake may have multiple explanations, including the acquisition by tumor cells of radiation resistance.

The orally available histone deacetylase inhibitor SAHA was studied in 16 DTC patients; no objective responses were reported, and most patients discontinued therapy due to adverse events. In a phase I trial, combining valproic acid, a histone deacetylase inhibitor, with 5-azacytidine, a DNA methylation inhibitor, was well tolerated; two patients with metastatic PTC demonstrated prolonged stable disease but radioiodine uptake was not assessed.

One of the first multicenter thyroid cancer trials sponsored by the National Cancer Institute, a phase II study of the DNA methylation inhibitor decitabine to attempt to restore radioiodine uptake in advanced DTC is led by M.D. Anderson investigators. Study recruitment has concluded, and a report is currently in preparation.

Summary

Compared with the dismal historical track record, the recent proliferation of clinical trials for thyroid cancer has been remarkable. (Continued on page 4)

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Targeting angiogenesis (and specifically VEGF receptors) has produced the most impressive clinical responses to date in DTC. Although most small molecule VEGF receptor antagonists also inhibit RET, the efficacy of axitinib to induce objective responses in the absence of any anti-RET activity suggests that RET may not be as important a target for therapy as VEGFR. Studies of therapies targeting nuclear mechanisms of gene regulation indicate that reversal of epigenetic or nuclear receptor abnormalities can potentially re-establish the cellular capacity to take up radioiodine, but the clinical significance of such an effect appears limited.

In collaboration with other M.D. Anderson investigators, our endocrinologists have focused on the earliest stages of drug development for advanced DTC. We currently participate in several phase I trials of novel therapies, such as PLX4032, a selective inhibitor of RAF kinases. Patients whose tumors bear the BRAF mutation and with advancing metastatic disease despite standard therapies can be enrolled in this trial, testing the hypothesis that inhibiting the mutant protein that is believed to cause the cancer could effectively treat the disease. Other drugs in phase I trials of interest for patients with DTC include novel inhibitors of VEGFR, MAPK signaling, and other key intracellular pathways. Based on such phase I experience, we are leading a new international phase II study of E7080, a novel inhibitor of VEGFR that also blocks angiogenesis that is stimulated by fibroblast growth factors, another important mechanism in DTC.

The overall goal of developing new treatments is to extend the duration of life without unduly harming the quality of that life. Presently, no novel treatment has been demonstrated to improve survival for thyroid cancer patients. Toxicities of many

of these new therapies, although less life-threatening than cytotoxic chemotherapies, are common and can be dose-limiting, and clinicians must be familiar with recognizing and managing the side effects if they intend to use these agents. Finally, the low rate of partial response, and the absence of complete responses in all of the various monotherapy trials identify the need to develop either more effect single agents or to identify rational combinations of therapeutic targets (including cytotoxic chemotherapies) that have synergistic effectiveness without enhanced cross-toxicities.

Information on these and other clinical trials for thyroid cancer at M.D. Anderson can be obtained at:

<http://www.mdanderson.org/departments/endocrinology/dIndex.cfm?pn=54DC0D15-EDFD-4394-82DBAD4EAABEACD6>

Trials active at other institutions can be also be found at:

www.clinicaltrials.gov or www.thyroid.org

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Notes from the Endocrine Faculty Team



Dr. Gilbert Cote promoted to professor

Dr. Cote earned his Ph.D. in Biochemistry from the University of Vermont Medical School and did his postdoctoral training in Molecular Endocrinology at Baylor College of Medicine before joining M. D. Anderson's Department of Endocrine Neoplasia and HD's faculty in 1992. Since then he has published numerous manuscripts and reviews on the topic of medullary thyroid cancer,

and currently holds membership at the Faculty of Medicine 1000 where he provides expert review of the thyroid cancer literature. In addition, he is recognized for his expertise in the study of aberrant RNA splicing and the role that errors in this pathway may play in the contribution to tumorigenesis. It is important to note that in addition to his research interests Dr. Cote is dedicated to mentoring and education. He has been a member of the Graduate School of Biomedical Sciences at Baylor College of Medicine since 1993 where he teaches several graduate level courses. In 2004 he was awarded the John P. McGovern Outstanding Teacher Award in recognition of his efforts. He is currently the Director of the Program in Human and Molecular Genetics at the GSBS. In honor of his accomplishments, Dr. Cote was promoted to professorship at M. D. Anderson in September of 2008.



Dr. Anita Kuo Ying joins the faculty

Dr. Anita Kuo Ying obtained her bachelor of arts degree from Rice University in Houston, Tx. She then left her hometown to obtain her medical degree from Duke University School of Medicine, where she also did her combined internal medicine/pediatrics residency. She accepted the position of Chief Resident in Pe-

diatrics for the following year. After 10 years in North Carolina, Dr. Ying returned to Houston to complete a dual adult and pediatric endocrinology fellowship at Baylor College of Medicine and M.D. Anderson Cancer Center. During that time, she developed an interest in clinical outcomes and effectiveness. She has presented her work on health care costs and has written a review on thyroid cancer in young adults. Dr. Ying is extremely excited to join the faculty at M.D. Anderson to pursue her clinical and research focus on benign and malignant endocrine tumors in children and adults, cancer survivorship, long-term endocrine effects of cancer therapy, and clinical effectiveness.

Surgical Management of Differentiated Thyroid Cancer: From Minimal Invasive to Aggressive (Appropriate) Surgical Management

**Gary L. Clayman, D.M.D., M.D., F.A.C.S., Professor
Department of Head and Neck Surgery**



By far, most thyroid masses are benign and do not require surgical management unless patients are symptomatic from the mass itself or pathology cannot be conclusively established without complete removal of the mass. Of the malignancies which may develop within the thyroid, approximately 80% will be papillary thyroid cancer (and its variants) followed by follicular thy-

roid cancer in 10% and then the rarer neoplasms of medullary and other less typical thyroid histologies.

Surgery is the mainstay of effective therapy among our current available armamentarium against these malignancies. Surgery must be well planned, thoughtful, beautiful/artistic, and address all known locations of disease within the thyroid bed, as well as the lateral necks, and superior mediastinum when disease has spread. All clinically and radiographic evidence of disease should be removed, whenever feasible, in the thyroid cancer patient's initial surgical procedure. Nevertheless, a prospective study by the American College of Surgeons showed that among over 5500 patients undergoing their initial surgery for Stage I and II differentiated thyroid cancers, 11% had persistent (unremoved evidence of cancer) following their initial surgery. This somewhat alarming statistic therefore requires thoughtful consideration (1).

Surgical Planning

The evaluation of a patient with thyroid cancer requires a comprehensive evaluation. The broad spectrum of patients range from early childhood to those of advanced age and the overall patient must be managed based upon their medical conditions and general health. The female predominance among patients with differentiated thyroid cancer requires consideration of issues including the potential for pregnancy.

The preoperative medical evaluation of the differentiated thyroid cancer patient requires analysis of thyroid function, a chest radiograph, and a comprehensive high resolution ultrasound of the thyroid bed and lateral necks. This ultrasound is critical in the surgical planning and studies at M.D. Anderson suggest that thoughtful use of this modality will drastically reduce the incidence of persistent (unaddressed) disease described earlier in the American College of Surgeons study (2). CAT scans or other imaging of the neck are rarely indicated except when diffuse disease is noted in the necks ultrasonographically, masses are minimally mobile, or among patients with recurrent or persistent disease. Fine needle aspiration cytology is required to analyze abnormalities found on ultrasound that would change the extent of surgery.

The Art of Thyroid Surgery

Thyroid surgery is truly an artform. Surgery must beautifully find the "sculpture within the stone" sparing all uninvolved structures. The thyroid gland rests in the central neck immediately beneath the cartilage of the voice box, extending

around the trachea (breathing tube) and esophagus (swallowing tube). The thyroid gland lies beneath fine musculature called "strap muscles" which are involved in swallowing (by pulling and lifting the voice box) as well as fine vibrato singing. Critical nervous structures also run beneath the thyroid including the superior laryngeal and recurrent laryngeal nerves controlling both sensation and motor function of the voice box, respectively. Additionally, the parathyroid glands, not part of the thyroid gland, usually lie immediately adjacent to the thyroid gland, possess the same blood supply of the thyroid gland, and control the homeostasis of calcium within the body. Thyroid surgery, therefore, is an artful, delicate dissection which identifies and spares all of the structures surrounding the thyroid thus providing safe removal of the gland. Dissection is performed with magnification either in the form of surgical optics, endoscopic instruments and even microscopes, depending on the circumstances or approach being utilized.

The Choice of Partial Versus Total Thyroidectomy

The indications for removal of all or part of the thyroid gland is a topic of frequent debate and controversy. Issues involved in arriving at the conclusion include consideration of the patient age, size of the mass (or masses), pathologic diagnosis, the ability of the patient to maintain thyroid hormone levels with medication, presence of lymph node(s) or other metastases, the utility of adjunctive radioactive iodine therapy as well as the desire to monitor blood levels of markers of their thyroid cancer.

Removal of half of the thyroid gland, (partial thyroidectomy) in patients with thyroid cancer, is occasionally only recommended in selected instances including when the patient is young (<45 years of age), there is a solitary thyroid cancer mass, the mass is 1.5cm or less in size, and there is no evidence of metastatic lymph nodes. Even when all of those criteria are met, although the survival from the cancer is equivalent independent of patients undergoing partial versus total thyroidectomy, the risk of recurrence or second primary tumors within the thyroid bed in the partial thyroidectomy group approaches 15 percent, however (3,4).

Partial thyroidectomy, nevertheless, facilitates thyroid hormone replacement but reduces the ability to monitor thyroglobulin (the blood protein assessed in differentiated thyroid cancers).

Total thyroidectomy, the preferred surgical procedure for patients greater than 45 years of age and possessing malignancies greater than 1.5cm, has a greater risk of permanent dysfunction of parathyroid function (the glands which control calcium levels in the blood) and should be performed in nearly all patients with evidence of metastases to lymph nodes or distant sites.

Neck Dissection for Metastatic Lymphadenopathy

Removal of lymph nodes from the lateral neck or those from the area beneath the thyroid gland are generally not performed electively unless there is ultrasonographic or other radiographic evidence of spread to those regional lymph nodes.

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Our approach, at M.D. Anderson, utilizes ultrasound guided fine needle aspiration cytology to determine whether metastatic lymph nodes are present and therefore require removal.

Quite predictably, thyroid cancers spread to lymph nodes in the neck regions described as the jugular chain, spinal accessory lymph nodes, posterior carotid lymph nodes, as well as paratracheal and superior mediastinal lymph nodes. The latter two sites may not be appreciated on preoperative ultrasound due to "shadowing" by the intact thyroid gland and sternum. However, these lymph node basins should be inspected during thyroid cancer surgery and if abnormalities are noted, electively dissected.

Neck dissection for metastatic lymph nodes is, once again, an artful preservation of all uninvolved muscular, vascular, and neural structures of the neck. Thus, the surgery removes primary fibrous, lymphatic, and fatty contents for pathologic analysis. The cosmetic and functional outcome is generally very acceptable to almost all patients. Self motivated physical therapy exercises for both shoulder and neck range of motion should be strongly recommended in all patients undergoing neck dissection.

Surgical Management of Aggressive (Deeply Invasive) Thyroid Carcinoma

Although uncommon, some patients develop deeply invasive thyroid cancers that involve critical structures such as the recurrent or superior laryngeal nerves, trachea, esophagus, or great vessels of the neck. The premise of surgery, again, requires a comprehensive excision of the invasive malignancy, but should also spare anatomically uninvolved structures. Even when these malignancies are deeply invasive into the thyroid cartilage, trachea, or esophageal muscularis, a functional organ sparing surgery can usually be performed. Reconstruction may range from requiring no augmentation to extensive microvascular approaches when defects are large and communicating with the aerodigestive tract.

If patients are approaching their fifth or later decades of life and a subsequent "organ sparing" surgery cannot further be performed, adjunctive radiation therapy (external beam) must be strongly considered. The surgeon who performed the surgery is the most informed in making this critical decision. The combined approach of comprehensive surgical excision of aggressive thyroid cancers with external beam radiotherapy achieves cervical (local / regional) control in greater than 90% of these patients when reduced to microscopic disease. The long term effects of external beam radiation therapy must be well understood and therefore this modality must be used quite judiciously (5).

Surgery For Recurrent Thyroid Cancer

Surgical management of recurrent differentiated thyroid cancer is a delicate balance of knowledge of the disease process, patient education, thoughtful intervention, and meticulous surgery. The basic tenets of the surgical management of these malignancies do not differ from those of previously untreated patients, although the surgery can be far more difficult and time consuming. The surgeries, nevertheless, can be safely performed by individuals which emphasize this type of surgery within their practice (6).

New Innovations Surgical Approaches

Over the past eight years, new surgical advances have allowed for innovative approaches for thyroid surgery. Video-assisted thyroid (VAT) surgery is now somewhat commonplace. The VAT provides excellent visualization and magnification up to 17 fold. Although VAT can be performed through a variety of incision locations, the cervical location is still preferred and is usually about 2.5cm in length. VAT is indicated for thyroid masses not exceeding 2cm in greatest dimension and overall glands not exceeding 30 cubic centimeters in overall volume (although minor modifications of the technique can adjust for slightly more voluminous glands). VAT has been performed on thousands of patients with results shown to be equivalent to open thyroidectomy in a randomized controlled study (7, 8).

The next advance in thyroid surgery has been the robotic thyroidectomy. Advantages of robotic thyroidectomy include even greater visualization as compared to VAT, incision location remote from the cervical area utilizing axillary or submammary incisions, ability to perform surgery by a single surgeon without assistance, as well as a three dimensional optical visualization as compared to the VAT (9).

Neither of these innovative approaches should be utilized for patients with known metastatic disease in the cervical region. Both, however, have significant advantages in selected patients and should be considered when the surgeons ability, patient desires, and disease process are all compatible.

Summary

Surgery remains a mainstay in the management of patients possessing differentiated thyroid malignancies. Thoughtful preoperative evaluation and interdisciplinary management, in conjunction with meticulous surgery, are the ingredients for optimal patient outcomes.

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New Clinical Trials

A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly

This goal of this clinical research study is to compare an investigational treatment for acromegaly against the standard treatment for acromegaly. Pasireotide long-acting release (LAR), which is also known as som230 LAR, will be compared against Sandostatin® LAR (octreotide LAR). Researchers want to learn if pasireotide LAR can help to control acromegaly. The safety of pasireotide LAR will also be studied.

This is open to patients with active acromegaly demonstrated by a lack of suppression of GH nadir to $< 1 \mu\text{g/L}$ after an oral tolerance test with 75 g of glucose (OGTT) (not applicable for diabetic patients) or a mean GH concentration of a 5-point profile within a 2 hour time period of $> 5 \mu\text{g/L}$ AND an elevated circulating IGF-1 concentration (age and sex adjusted). Patients who received pasireotide (SOM230) prior to randomization or have had pituitary irradiation within the last 10 years may not be considered.

For more information, please contact Pat Degen, Research Nurse Supervisor, at 1-713-792-2396

A Phase II trial of Sunitinib (SU11248) in Iodine-131 refractory, unresectable medullary thyroid cancers

The goal of this clinical research study is to learn if sunitinib can help control thyroid cancer that has spread outside the thyroid. The safety of this drug will also be studied.

This study is for adults diagnosed with medullary thyroid carcinoma. The patient's disease must have progressed despite treatment with iodine-131 therapy or they cannot be candidates for iodine-131 therapy, as well as their malignancy could not be removed by surgery. They must have radiographically or biochemically measurable disease, and cannot have received prior receptor tyrosine kinase inhibitors or external beam radiation to the tumor region.

For more information, please contact Cheryl Mize, Research Nurse, at 1-713-792-2840 for further information.

These trials are NCI sponsored trials and cannot be administered outside of a NCI designated cancer center.

For information on other clinical trials conducted at M. D. Anderson Cancer Center, please visit: http://www.mdanderson.org/Cancer_Pro/CS_Resources/display.cfm?id=562561A1-751F-11D4-AEBD00508BDCCE3A&method=displayFull. For information on other clinical trials conducted at other institutions, please visit: <http://www.clinicaltrials.gov/>

Wish to refer a patient to M. D. Anderson?



Online Referrals:

M. D. Anderson has created an online referral process, *myMDAnderson*, to help you get your patient into M. D. Anderson as quickly as possible. You can use *myMDAnderson* to follow the treatment your patients receive by viewing transcribed reports and accessing your patients' schedules. To qualify for this free service, you must be a licensed, practicing physician. To start a referral through *myMDAnderson*, please access this portal: <https://my.mdanderson.org/public/physicians/user/>

Telephone Referrals:

Physician to Physician referrals to the Dept of Endocrine Neoplasia and HD, please call 713-792-2841. New Patient Referral Coordinators, please call 713-563-4400.

Thyroid Cancer Care at M. D. Anderson - Not Just for Adults

Steven G. Waguespack, M.D., Associate Professor, Dept. of Endocrine Neoplasia and Hormonal Disorders



Malignant neoplasms of the thyroid are rare in the pediatric population, with an incidence of ≤ 1 case/million/year in children under ten years of age to 15.4 cases/million/year in adolescents ages 15-19, which is the most commonly affected pediatric age group. Over 90% of thyroid cancers occurring in childhood are papillary thyroid cancer (PTC), a well-differentiated tumor arising from the thyroid follicular epithelium. For reasons that remain unclear, children with PTC present with a higher frequency of lymph node and pulmonary metastases as compared with adults. Despite their more advanced clinical presentation, children diagnosed with PTC have an excellent prognosis. Although recurrences are higher in children, survival over decades is generally the norm. Part of this clinical phenomenon may be due to mutational differences between children and adults, in addition to the fact that pediatric PTC is usually very iodine avid, typically leading to successful treatment of metastatic disease after one or more courses of radioactive iodine (RAI) therapy. Very rarely, children with PTC have progressive distant metastatic disease that no longer responds to RAI. In such cases, systemic therapy is contemplated, with the use of oral tyrosine kinase inhibitors considered in appropriate patients. Most children with PTC do not typically

require aggressive treatment in childhood because their disease is usually indolent and almost always responds well to standard therapeutic approaches. Therefore, treatment aggressiveness must always be weighed against the possible life-long side effects. Although children with PTC are usually treated the same as adults, the disease process and risk for treatment side effects is unique enough that pediatric patients benefit from treatment in centers that can offer multidisciplinary expertise in the care of children with thyroid malignancies.

The University of Texas
M. D. Anderson Cancer Center
Endocrine Neoplasia and Hormonal Disorders - Unit 1461
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Announcements

Visit us at Booth #717!



Please come and visit the Dept of Endocrine Neoplasia and HD's exhibit at the upcoming AACE (American Association of Clinical Endocrinologists) meeting from May 13-17, 2009 at the Hilton Americas Houston and the George R. Brown Convention Center here in Houston, TX. Come and learn about our cutting edge patient care, research, innovative programs, numerous specialties united under one umbrella and home to one of the largest clinical trial programs in the nation. You'll get to meet with some of our renowned physicians, researchers, and mid-level providers.

Interested in four decades of very unique clinical data gathering? The Atlas of Endocrine Neoplasia book will also be displayed at our booth and also available for a free drawing.

Book: Atlas of Endocrine Neoplasia

By Mouhammed Amir Habra, M.D., and Rena Vassilopoulou-Sellin, M.D.

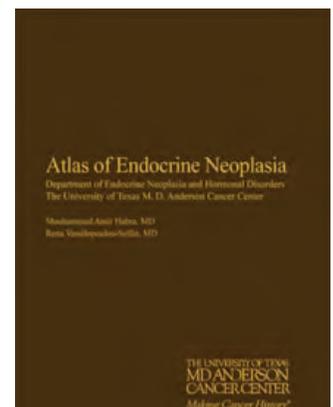
With many endocrine tumors being relatively uncommon, it is exceedingly hard to find clear documentation of the natural course of these tumors and their clinical presentation. This book has documented four decades of very unique clinical data gathering combined with the most recently used tests and diagnostic procedures to make it an unparalleled resource for physicians in practice as well as those in training.

It comes in a leather bound cover with 167 pages containing approximately 700 pictures and colored illustrations. In addition, this atlas provides relevant text, tables and algorithms to make it a comprehensive, yet concise, reference for endocrine neoplasia.

This atlas provides a detailed coverage of endocrine neoplasms including the epidemiology, clinical features, diagnostic procedures and treatment. This classical compilation is intended to serve as a reference for physicians as well as medical students and trainees who can see the natural course of various clinical syndromes and endocrine tumors. In addition, it summarizes the diagnostic work up and the interpretation of wide variety of endocrine tests currently in clinical use.

To Order:

Please visit: <http://www.mdanderson.org/publications/neoplasia/> for an order form or call 713-792-2841.



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