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Thyroid neoplasms are classified into three major categories: epithelial, nonepithelial, and secondary. Most primary epithelial tumors of thyroid are derived from follicular cells. These include follicular adenoma and carcinoma (Hürthle and non-Hürthle), and papillary carcinoma and its variants. Other primary epithelial tumors include medullary carcinoma, mixed medullary and follicular carcinomas, insular and poorly differentiated carcinoma, anaplastic carcinoma, and the least common squamous carcinoma and related tumors. The nonepithelial tumors are rare; the most common include malignant lymphoma and tumors arising from the mesenchymal elements. The secondary tumors represent metastatic tumors to the thyroid usually originating in lung, kidney, and breast. In this article, the authors review the unusual tumors of the thyroid, their morphologic features, and clinical and prognostic implications.

Genome-Wide Studies in Thyroid Neoplasia	311
Thomas J. Giordano	

There is much interest in the application of genome biology to the field of thyroid neoplasia, despite the relatively low mortality rate associated with thyroid cancer in general. The principal reason for this interest is that the field of thyroid neoplasia stands to benefit from the application of genomic information to address a variety of

pathologic and clinical issues. In addition to practical patient care issues, there is an excellent opportunity of expand the basic understanding of thyroid carcinogenesis. In this article, the most relevant genomic work on thyroid tumors performed to date is reviewed along with some general comments about the potential impact of genomic biology on thyroid pathology and the management of patients with thyroid nodules and cancer.

Intragenic Mutations in Thyroid Cancer

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Manuel Sobrinho-Simões, Valdemar Máximo, Ana Sofia Rocha, Vitor Trovisco, Patricia Castro, Ana Preto, Jorge Lima, and Paula Soares

The close genotype-phenotype relationship that characterizes thyroid oncology stimulated the authors to address this article by using a mixed, genetic and phenotypic approach. As such, this article addresses the following aspects of intragenic mutations in thyroid cancer: thyroid stimulating hormone receptor and guanine-nucleotide-binding proteins of the stimulatory family mutations in hyperfunctioning tumors; mutations in RAS and other genes and aneuploidy; PAX8-PPAR γ rearrangements; BRAF mutations; mutations in oxidative phosphorylation and Krebs cycle genes in Hürthle cell tumors; mutations in succinate dehydrogenase genes in medullary carcinoma and C-cell hyperplasia; and mutations in TP53 and other genes in poorly differentiated and anaplastic carcinomas.

Dysregulated RET Signaling in Thyroid Cancer

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Maria Domenica Castellone and Massimo Santoro

Numerous biologic processes and such diseases as cancer depend on activation of tyrosine kinase receptors. The RET tyrosine kinase receptor was discovered two decades ago as a transforming gene and was subsequently implicated in the formation of papillary and medullary thyroid carcinoma. This article examines the data about the mechanism of activation of downstream signal transduction pathways by RET oncoproteins. Collectively, these findings have advanced the understanding of the processes underlying thyroid carcinoma formation.

Dysregulation of the Phosphatidylinositol 3-Kinase Pathway in Thyroid Neoplasia

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John E. Paes and Matthew D. Ringel

The phosphatidylinositol 3-kinase (PI3K) signaling pathway is an important regulator of many cellular events, including apoptosis, proliferation, and motility. Enhanced activation of this pathway can occur through several mechanisms, such as inactivation of its negative regulator, phosphatase and tensin homolog deleted on chromosome ten (*PTEN*), and activating mutations and gene amplification of the gene encoding the catalytic subunit of PI3K

(*PIK3CA*). These genetic abnormalities have been particularly associated with follicular thyroid neoplasia and anaplastic thyroid cancer, suggesting an important role for PI3K signaling in these disorders. In this article, the role of PI3K pathway activation in thyroid cancer is discussed, with a focus on recent advances.

Epigenetic Dysregulation in Thyroid Neoplasia

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Tetsuo Kondo, Sylvia L. Asa, and Shereen Ezzat

Gain-of-function mutations in oncogenes have aided our understanding of the molecular mechanisms of thyroid carcinogenesis. Mutations or deletions cause inactivation of tumor suppressor genes in thyroid carcinomas. However, recent advances have disclosed the significance of epigenetic events in the development and progression of human tumorigenesis. Indeed, various tumor-suppressor genes and thyroid hormone-related genes are epigenetically silenced in thyroid tumors. This article reviews the evidence for epigenetic gene dysregulation in follicular cell-derived thyroid carcinomas including papillary thyroid carcinoma, follicular thyroid carcinoma, and undifferentiated thyroid carcinoma. The authors also discuss future applications of epigenetics as ancillary diagnostic tools and in the design of targeted therapies for thyroid cancer.

Sonographic Imaging of Thyroid Nodules and Cervical Lymph Nodes

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Stephanie A. Fish, Jill E. Langer, and Susan J. Mandel

The initial application of sonography for the evaluation of the neck, more than 30 years ago, was to differentiate cystic and solid thyroid nodules. With improvements in technology, ultrasound has been applied to characterize distinct features in the appearance of thyroid nodules. More recently, its function has been expanded to assess cervical lymph nodes for metastatic thyroid cancer. This article discusses the sonographic features of thyroid nodules associated with malignancy and the role of ultrasound in the management of patients with thyroid cancer.

Follow up Approaches in Thyroid Cancer: A Risk Adapted Paradigm

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R. Michael Tuttle and Rebecca Leboeuf

The primary goal in the follow up of thyroid cancer patients is to identify and treat persistent and recurrent disease at a time that minimizes morbidity and disease specific mortality. This article presents a risk-adapted follow-up paradigm to guide both intensity and methodology of follow-up testing based on initial risk stratification, ongoing risk stratification, and secondary risk stratification that incorporates each of the well-known risk factors for recurrence and death from thyroid cancer, with a response to therapy variable as well as duration of disease-free survival. With a

proper understanding of the biology of the disease and with accurate assessments of response to therapy, clinicians are better able to tailor a risk-appropriate follow-up approach to individual patients, minimizing excessive testing while still providing adequate testing to detect clinically significant disease recurrence in a timely fashion.

Surgical Approaches to Thyroid Tumors

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Jessica E. Gosnell and Orlo H. Clark

This article includes discussions of the surgical approach to benign and malignant disease and the role of prophylactic thyroidectomy and nodal dissection for medullary thyroid cancer. The controversy regarding the extent of dissection for differentiated thyroid cancer and the role of lymph node dissection are reviewed also. A description of the authors' surgical technique for thyroidectomy is detailed. Finally, several emerging technologies are introduced.

An Updated Systematic Review and Commentary Examining the Effectiveness of Radioactive Iodine Remnant Ablation in Well-Differentiated Thyroid Cancer

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Anna M. Sawka, James D. Brierley, Richard W. Tsang, Lehana Thabane, Lorne Rotstein, Amiram Gafni, Sharon Straus, and David P. Goldstein

Radioactive iodine remnant ablation (RRA) is used to destroy residual normal thyroid tissue after complete gross surgical resection of papillary or follicular thyroid cancer. The article updates a prior systematic review of the literature to determine whether RRA decreases the risk of thyroid cancer-related death or recurrence at 10 years after initial surgery, including data from 28 studies. No long-term randomized trials were identified, so the review is limited to observational studies. The incremental benefit of RRA in low risk patients with well-differentiated thyroid cancer after total or near-total thyroidectomy who are receiving thyroid hormone suppressive therapy remains unclear.

Management of Medullary Thyroid Carcinoma

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Camilo Jiménez, Mimi I-Nan Hu, and Robert F. Gagel

Medullary thyroid carcinoma (MTC) is responsible for 13.4% of the total deaths attributable to thyroid cancer in human beings and research on MTC over the last 40 years has identified the RET proto-oncogene as a very relevant component of development of both sporadic and hereditary MTC. An activating germline RET proto-oncogene mutation responsible for a multiple endocrine neoplasia syndrome type 2 (MEN2) or a familial hereditary MTC syndrome is carried by 25% to 35% of patients with MTC. The recognition of RET proto-oncogene mutations by genetic sequencing has allowed us to differentiate hereditary from sporadic MTC, so that it is now possible to identify and treat children at risk for

this disease before development of metastasis. Thanks to this discovery, we can now establish the association of MTC with other tumors in the context of MEN2 syndrome; determine adequate follow-up, prognosis, and treatment for patients with hereditary disease; and use this information to develop new therapies against both sporadic and hereditary MTCs.

External Beam Radiation Therapy for Thyroid Cancer

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James D. Brierley and Richard W. Tsang

This article discusses the role of external beam radiotherapy (XRT) in the management of well-differentiated thyroid cancer (WDTC), medullary thyroid cancer, and anaplastic thyroid cancer. Although there are no randomized controlled studies on the use of XRT in thyroid cancer, evidence supports its use to treat gross disease after surgery or unresectable cancer and its use as an adjuvant after resection of a known high-risk disease in WDTC, and, to a lesser extent, in medullary thyroid cancer. The use of XRT for the palliation of symptomatic disease and recent advances in the technology of radiation delivery also will be discussed.

Early Clinical Studies of Novel Therapies for Thyroid Cancers

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Steven I. Sherman

Historically, systemic therapies for advanced, metastatic thyroid carcinomas have been poorly effective. However, as a result of a confluence of increasing knowledge of the biologic basis for thyroid cancer development and progression, identification of therapeutic agents that could target these biologic abnormalities, and enthusiasm for research by both funding agencies as well as patients, multiple clinical trials have been initiated and successfully completed during the past several years. This article focuses on findings from key studies that reflect the new paradigms for treatment.

Anaplastic Thyroid Cancer

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Ryan L. Neff, William B. Farrar, and Richard T. Kloos

Guest Editor: Kenneth D. Burman

Anaplastic thyroid cancer is an uncommon, typically lethal malignancy of older adults with no effective systemic therapy. The mean survival time is usually less than 6 months from the time of diagnosis and, unfortunately, this outcome is not fundamentally altered by available treatments. Histologic tissue confirmation is recommended if the diagnosis is not absolutely certain to exclude tumors with better prognosis or that require different treatment. Patency of the airway should be kept in mind throughout the patient's course and individuals with impending airway obstruction, in the absence of imminent death from other sites of disease, should be considered for a tracheostomy to secure the airway. Enrollment in meaningful clinical trials should be given the highest priority at all decision points.

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