Frontiers in Thyroid Cancer: December 2009

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THE INCIDENCE OF THYROID CANCER is rising rapidly in the United States and worldwide. Thanks to the efforts of many investigators and clinicians, research advances in laboratory and clinical science are now being translated into the clinical management of patients with thyroid cancer. These important advances continue to lead to new research questions from basic science to clinical management, as well as to new clinical trials. For a special section of this issue of *Thyroid*, we asked a number of thyroid cancer experts to bring readers up to date on several areas critical to advancing the understanding of thyroid carcinogenesis and better clinical management. Their review articles give readers a look at exciting new research tools, recently identified oncogenes, advances in patient management and clinical trials, and promising new directions for research in thyroid cancer.

The emerging science in the areas of thyroid stem cells, thyroid cancer stem cells, and side populations represents an exciting area of research. Klonisch *et al.* (1) not only review the potential role that thyroid stem cells play in thyroid gland development but also discuss how these cells may be involved in resistance to cancer-directed therapies and thyroid regeneration. Kim and Zhu (2) summarize the existing mouse models of differentiated thyroid cancer and highlight the similarities and differences in the phenotypic characteristics of the genetically engineered mice. They show how these models have led to identification of novel oncogenes and elucidation of *in vivo* molecular actions that mediate thyroid carcinogenesis. In addition to genetic models, xenograft models in immunocompromised mice are now used as preclinical models for thyroid cancer therapy. In their review, Kim and Zhu (2) delineate the strengths and limitations of these systems in detail.

In vitro cell-based studies of human and nonhuman thyroid cell lines have led to a better understanding of thyroid regulatory mechanisms and helped identify key regulatory pathways that govern the biology of thyroid cancer cells. As reviewed by Pilli *et al.* (3), critically important information regarding cancer cell biology has been gained from studies using thyroid cells, but the results must be interpreted with care because of the inherent limitations of these systems. It is crucial for investigators using these preclinical systems, and for readers interpreting research results, to fully understand

the advantages and pitfalls of the various *in vivo* and *in vitro* model systems. In addition, one must consider the potential impact side populations may have in determining responses to cancer-inducing or cancer-inhibiting challenges. The articles on thyroid stem cells, mouse models of cancer, and tumor cells expertly address experimental studies of thyroid cancer and set the stage for the more clinically directed articles in the issue.

While somatic mutations can be identified in most primary thyroid cancers, the identity of genes predisposing for the development of thyroid cancer is less certain. Because papillary thyroid cancer appears to be highly heritable in some populations, several research groups are interested in discovering the predisposing genes for its development, including those genes that may have low penetrance. Identifying genes that predispose to thyroid cancer may transform risk assessment for individual patients in the future. As reviewed by Vriens *et al.* (4), several groups have identified genes or gene loci associated with papillary thyroid cancer in families and in large populations. Although the biological impact of these potential predisposing genes is not yet certain, somatic mutations in *BRAF*, *RAS*, and *RET* gene rearrangements are well-defined thyroid cancer-causing genetic changes. The presence of these alterations and the differential expression of specific mRNAs and microRNAs have been used to classify thyroid tumors. Recently, several groups have applied analysis of common thyroid cancer-related gene mutations and profiles of mRNA and microRNA expression to thyroid nodule fine-needle aspiration samples to improve preoperative characterization. Nikiforova and Nikiforov (5) review the advances in molecular diagnostics and predictors of thyroid cancer and discuss application of these procedures to clinical practice.

In addition to cytopathology and molecular analysis, ultrasound is another tool to characterize thyroid nodules. The expansion of thyroid ultrasound into everyday clinical practice has led to identification of many thyroid nodules that previously would have eluded clinical detection. Sipos (6) reviews the utility of ultrasound to classify nodules into risk categories for cancer. Additionally, she examines how ultrasound can be used to define the extent of primary surgery for thyroid cancer and to identify and treat recurrent or residual

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thyroid cancer within the neck. The extent of initial surgery for patients with papillary thyroid cancer is highly debated, particularly the role of so-called "prophylactic" central neck dissection for individuals without obvious nodal metastases. Sippel and Chen's comprehensive review of the data (7) brings into focus why the extent of surgery must be determined by balancing surgical risk against the likelihood of favorable patient outcomes. In the future this clinical decision may be guided by preoperative molecular analysis and imaging.

Following surgery for thyroid cancer, patients are often treated with radioiodine therapy. The risks and benefits of this treatment have been an ongoing focus of many research articles for decades. In his review, van Nostrand (8) expertly collates this information and provides a framework for clinicians to consider the need for ^{131}I and dosing strategies based on the rationale for treating individual patients.

After little progress in the field, clinical trials are now studying molecular targeting treatment options for patients with anaplastic thyroid cancer or those who have defined thyroid cancer metastases that progress despite ^{131}I therapy. In the final article of this special section, Schlumberger and Sherman (9) review recent data from clinical trials for patients with progressive thyroid cancer. They focus on several crucial aspects. These include efforts to 1) better define the correct patient population for enrollment in clinical trials, 2) determine the best therapeutic targets for progressive metastatic thyroid cancer, and 3) optimize design so that appropriate endpoints are measured to best identify activity that results in clinical benefit. Particularly interesting and important are the conundrums presented when using traditional measures to try to achieve sufficient statistical power for a study.

We have enjoyed bringing this special group of articles to the readers of *Thyroid* and hope they will find them timely and provocative. We believe the selected topics and their coverage by recognized experts will engage basic scientists, clinical researchers, and physicians caring for patients with thyroid cancer. It is essential that basic and clinical science develop

and grow together to improve the care and outcome of patients with thyroid cancer.

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