

## Foreword



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In this issue of *Endocrinology and Metabolism Clinics of North America*, Drs. Ezzat and Asa have compiled a remarkable list of authors and topics on thyroid tumors. The articles cover all of the aspects from a basic and practical point of view.

Drs. Baloch and LiVolsi describe the pathology of unusual thyroid tumors, both benign and malignant. Though papillary and follicular tumors are the most common, with medullary and anaplastic being the less common tumors, there is a large variety of very uncommon tumors, mostly nonepithelial thyroid tumors or secondary from other tissues.

As discussed by Giordano, there is a growing interest in genetic studies involving thyroid cancer. Genetic analysis allows for improving clinical diagnosis where the pathology may be confusing. Pharmacogenetics enables investigators to determine which patients will respond appropriately to certain therapies. Furthermore, genetic analysis enhances the possibility of identifying new therapeutic targets. There are examples of each of these in regard to thyroid cancer, including the over-expression of the MET oncogene in papillary tumors and the mutations of the Ret oncogene; the latter are a target for a specific tyrosine kinase inhibitor now in clinical trials. Molecular profiling should also be able to identify those well-differentiated tumors that are at high risk for recurrence and metastasis. Thus, the possibilities for the use of genetics are endless.

Extending the discussion on genetic mutations in various thyroid cancer types, Soares and coauthors present information on thyroid stimulating hormone receptor and Gs protein mutations in hyperfunctioning tumors, mutations in the *RAS* and *BRAF* genes, rearrangements of *PAX8-PPAR $\gamma$* ,

mutations in *OXPHOS* and Krebs cycle genes in Hürthle cell tumors, mutations in *SDH* genes in medullary carcinoma and C-cell hyperplasia, and mutations in *TP53* and other genes in poorly differentiated and anaplastic carcinomas. Each of these tumors demonstrates a genotype-phenotype relationship with the associated genes.

The RET tyrosine kinase is dysregulated in papillary and medullary cancers. Papillary thyroid carcinoma is associated with RET/PTC chromosomal rearrangements, whereas MTC features RET germline or somatic point mutations. Grb7/10 binding, inhibition of the tyrosine phosphatase SHP-1, and activation of phospholipase C $\gamma$  are some of the major signaling pathways in the RET oncogenic transformation of thyroid cells that result in tumor development. Castellone and Santoro, in addition to describing the above mechanisms of action, also discuss in detail other important pathways involved.

Paes and Ringel, on the other hand, describe in their article how the enhanced activation of the PI3K/Akt pathway is seen in follicular and anaplastic thyroid cancers. This may 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*).

Kondo, Asa, and Ezzat describe the epigenetic silencing of tumor-suppressor and thyroid-related genes in thyroid tumors. The effect may be seen with follicular-cell derived thyroid carcinomas, including papillary thyroid carcinoma, follicular thyroid carcinoma, and undifferentiated thyroid carcinoma. Now that DNA methylation inhibitors with histone deacetylase inhibitors have demonstrated utility in other tumors by re-expression of tumor suppressor genes, their use in certain thyroid cancers is a distinct possibility.

Tuttle and Leboeuf describe the evidence behind the rationale for the different approaches in the monitoring of patients who have differentiated thyroid cancer. They emphasize the role of thyroglobulin detection and the emerging utility of PET/CT imaging in identifying residual disease.

Thyroid sonography technology and usage has progressed enormously. As described by Fish, Langer, and Mandel, it is used today to characterize distinct features in the appearance of thyroid nodules to aid in the diagnosis, and to assess cervical lymph nodes, for metastatic thyroid cancer. In the former instance, characteristic sonographic appearance of a nodule can be helpful in determining which nodules should undergo fine needle aspiration, especially when the nodule is small or there are multiple nodules present. In the latter case, a heterogeneous appearance with calcifications or peripheral vascularity strongly suggests metastatic disease.

The use of tyrosine kinase inhibitors has proven to be partially effective in clinical trials in patients who have differentiated and medullary thyroid cancers. Most of the inhibitors affect the vascular endothelial growth factor receptor (VEGFR), and some also inhibit the RET protein. Their effectiveness suggests that the VEGFR may be more important than the RET. As Sherman points out, the partial effectiveness of the available agents, when used

in combination therapy and their ineffectiveness when used alone, requires that more specific and better agents be developed.

Medullary carcinoma and its therapy are described in the article by Jiménez, Hu, and Gagel. The presence of the RET oncogene mutations in the index cases, together with the use of serum calcitonin levels, has made the diagnosis of children with the disease much easier and allows for early preemptive therapy. Surgery is still the mainstay of treatment, and cases are followed using serum calcitonin levels to identify those with metastatic disease. Recently, the tyrosine kinase inhibitors have proven useful as inhibitors of the tumors, and there is hope that newer agents will be developed.

Neff, Farrar, and Kloos discuss anaplastic carcinomas. As is well known, it is a rapidly fatal disorder, often within six months of pathologic diagnosis, with no current therapy. Fortunately, it is rare. Apparently, it may develop out of a papillary (PTC) or follicular (FTC) cancer and is therefore the cause of death in certain cases of PTC and FTC. Though surgery may be necessary to protect the airway, and radiation therapy and chemotherapy are used, no therapy is currently of any real value. The authors plead for some new clinical trials to attempt to find some therapeutic modality that can alter the prognosis.

Sawka and coauthors reexamine the value of radioactive iodine for ablation of remnant thyroid in cases of well-differentiated cancer and find that the results are inconclusive and warrant controlled trials. External beam radiotherapy may be used to treat well-differentiated thyroid cancer, medullary, and anaplastic thyroid cancer. It can be used to control residual well-differentiated cancers after surgery and radioactive iodine, or may be the only effective therapy in some cases of anaplastic thyroid cancer and may be useful in metastatic thyroid cancer. However, as pointed out by Brierley and Tsang, controlled trials to determine its effectiveness have not been carried out.

Surgery is an important component of the therapy of thyroid tumors. Many centers with experienced and skilled surgeons show an extremely low rate of recurrent nerve palsy or hypoparathyroidism. Consequently, Gosnell and Clark suggest that total thyroidectomy should be considered even in patients who have benign disease. They argue that this avoids the necessity of repeat surgery and the inherent morbidity, and the ease of using replacement thyroid medication.

As the reader can see, the issue is extremely comprehensive and will become an important landmark for a number of years, thanks to the hard work of Drs. Ezzat and Asa, and the authors of each impressive article.

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