

# The Art of Endocrine Surgery

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I am fascinated by endocrine tumors. While I was a fellow at NCI, I was exposed to a variety of clinical syndromes and clinical problems associated with them; it was one of the highlights of my academic career. Because these cancers arise from relatively small organs, which secrete hormones with wide-ranging effects on the body, they cause physiologically unique syndromes. Moreover, they are almost always curable; you can take out a tumor and dramatically improve a patient's life.

I devote about 60 percent of my time to my surgical practice, and perform approximately 250 endocrine surgeries per year. The surgeries themselves are aesthetically pleasing; there is a real delicacy associated with the procedure, whether for adrenal or parathyroid tumors, thyroidectomies, or resection of islet cell tumors of the pancreas. Endocrine surgery also has a fascinating history, which my co-editors and I have

recently highlighted in an edited collection of surgical stories, *The Supreme Triumph of the Surgeon's Art: A Narrative History of Endocrine Surgery*. For example, the tiny parathyroid gland was first discovered (and then forgotten) through the meticulous surgical necropsy of an Indian rhinoceros. The rhinoceros was most likely killed by an elephant at the London Zoo and later examined by the prominent anatomist and Darwin-opponent, Sir Richard Owen in the mid-1800s.

The other 40 percent of my time is devoted to basic and translational research. In addition to our surgical team, we have a large molecular biology research group, comprised of scientists, postdoctoral fellows, and students, who use a variety of genomic platforms to study molecular markers associated with the diagnosis and prognosis of thyroid cancer. It is truly exhilarating to be a part of the search, discovery, and challenging statistical analyses associated with this line of research.



(Photo: Courtesy of M. Zeiger)

Martha A. Zeiger, M.D.

Thyroid cancers  
are the most  
commonly  
occurring  
endocrine tumor.

## Separating the Benign from the Malignant Thyroid Tumors

The thyroid resides at the base of the neck; it regulates cardiovascular function, temperature, and body weight. Thyroid cancers are the most commonly occurring endocrine tumor. For unknown reasons, their incidence has been steadily increasing over the past several decades; over 60,000 new cases were diagnosed in 2014. And, thyroid cancers range from one of the most indolent human cancers (papillary thyroid cancer) to one of the deadliest (anaplastic thyroid cancer).

We can tell a great deal about the diagnosis from clinical and histological features based on fine needle aspiration biopsies, but still many tumors remain indeterminate on biopsy without clear features of a benign or malignant lesion. Therefore, we and others are searching for molecular biomarkers that could add further precision to our ability to distinguish these tumors and allow us to tailor surgical operations appropriately.

There are a number of promising biomarkers under development. We have recently published encouraging results with DNA copy number variation for the diagnosis of follicular cancers (indistinguishable from benign adenomas by needle biopsy), and we are in the process of gathering data on prognostic markers for thyroid cancer as well. We are also studying microRNAs and mutations in *BRAF* in the prognostic evaluation of papillary thyroid cancer. Additional platforms

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that we study include methylation arrays and alternative splice variant analyses.

*BRAF* is an interesting example of the challenges that academic research faces in establishing the true clinical value of individual biomarkers with regard to predicting prognosis. Recently, we analyzed more than 200 patients from four academic centers and found that there was no association of *BRAF* with lymph node metastases. While studies from other investigators have suggested a link between *BRAF* mutations and papillary thyroid cancer outcomes, many studies have not. Many variables account for the differing conclusions and only large-scale, well-designed, prospective studies will ultimately validate prognostic utility. We are currently conducting this very research with three other academic centers.

Recently, I was part of the NCI Cancer Genome Atlas (TCGA) program to genotype 400 papillary thyroid cancers. The exciting data resulting from this comprehensive

analysis suggests that we will ultimately need to redefine thyroid cancer subtypes. That will be the first step towards developing new treatment options.

## Industrial Strength Cooperation

Our group has been involved with several companies in the development of molecular panels used for better thyroid nodule diagnosis. Many have very promising results and provide good negative and positive predictive information. Their use and impact in the context of a clinical setting has yet to be carefully evaluated and, many groups, including ours, are in the process of doing so. Researchers, clinicians, and biomedical industry ultimately seek the same thing—better diagnosis and better treatment for cancers. In order to tackle these clinical questions we need to work very closely together, carefully designing and evaluating molecular panels that are introduced into the market for clinical efficacy.

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