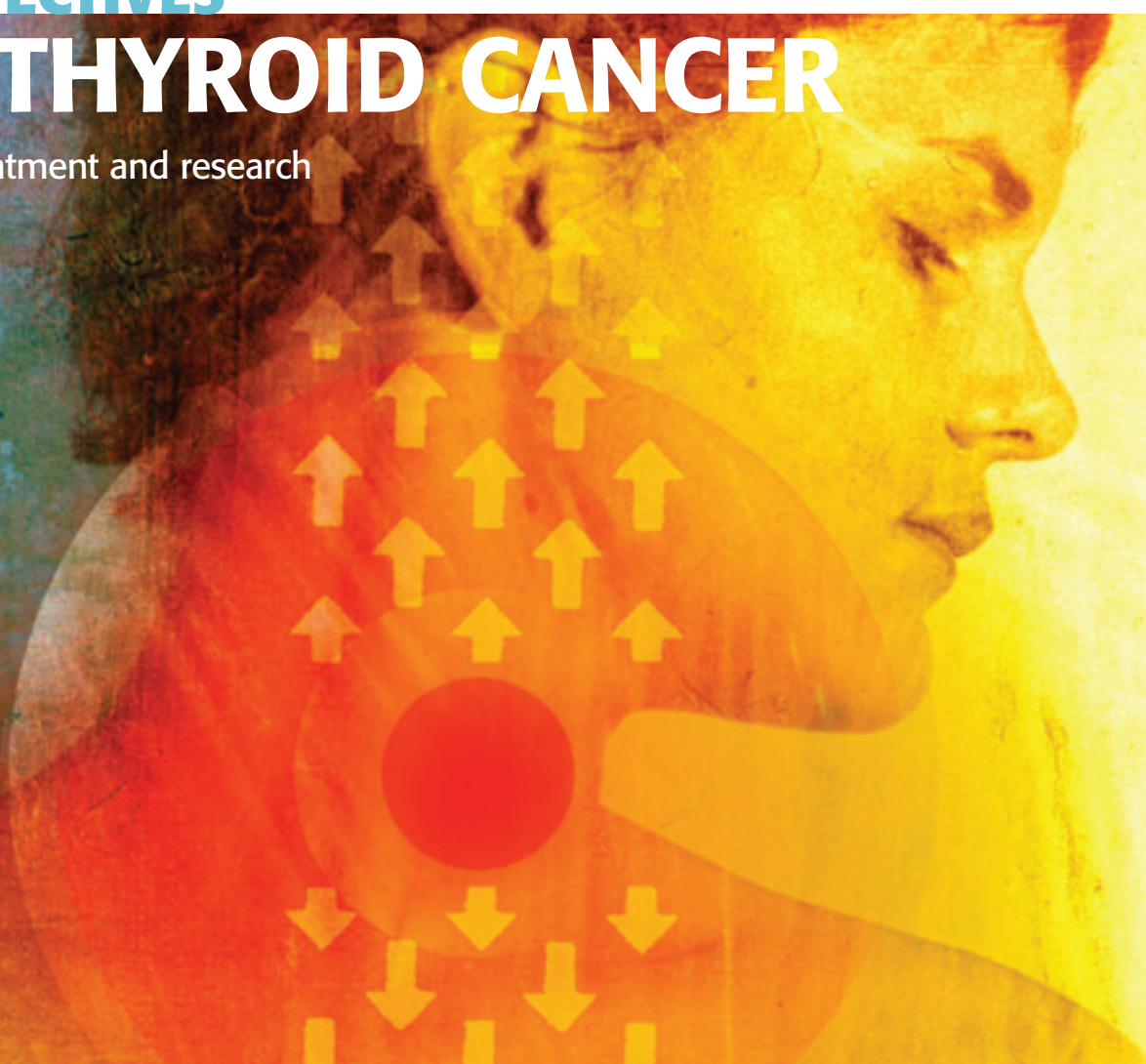


3 PERSPECTIVES ON THYROID CANCER

What's new in treatment and research



The incidence of thyroid cancer has been rising gradually over the past decade. After initial treatment with thyroidectomy, usually followed by adjuvant radioiodine ablation and thyroid hormone suppressive therapy, most patients will be cured and remain cancer free. However, persistent or recurrent disease is not uncommon. Drs. Tuttle and Mazzaferri discuss the rapidly evolving approaches to detect thyroid cancer recurrence, and the therapeutic challenges posed by the increased sensitivity of these new surveillance modalities. Current therapies are ineffective for those patients who have metastatic cancer unresponsive to surgery and radioiodine. Dr. Fagin discusses how the knowledge of the genetic origin of thyroid cancer is being used to design and test promising new therapies.



Giving the basic scientist's point of view is James A. Fagin, M.D., of the University of Cincinnati.



Giving the clinical scientist's point of view is Ernest L. Mazzaferri, M.D., M.A.C.P., of The Ohio State University and University of Florida.



Giving the clinical practitioner's point of view is Robert Michael Tuttle, M.D., of Memorial Sloan-Kettering Cancer Center.

From the Basic Scientist:

Targeted Therapies in Cancer

In several types of cancer, new therapies are being developed to interfere with the activity of oncoproteins thought to be important in causing disease. These compounds disrupt pathways inappropriately activated in cancer cells, leaving normal cells relatively unscathed. Protein kinases regulate signaling pathways that control critical cellular activities. Mutated kinases with unregulated activity often contribute to the development of cancer. If the cancer cell depends on the continued activity of the mutant enzyme for survival, compounds that selectively inhibit its function hold promise as therapeutic agents. Oncoproteins activated by gene mutations occurring very early in tumor progression likely remain the essential drivers of tumor expansion—even after accumulation of numerous additional genetic changes—and these should be prioritized as molecular targets. This premise is validated by the paradigmatic success of imatinib in

chronic myelogenous leukemia and in gastrointestinal stromal tumors, but remains to be proven as a general principle and in specific tumor types.¹ Among solid tumors, medullary thyroid carcinomas (MTC) and differentiated thyroid cancers represent excellent models in which to test this concept. This is because activating point mutations of the *RET* tyrosine kinase receptor gene in MTC occur early in tumor development, making the RET oncoprotein a promising target for pharmacological interference. Indeed, at least one compound that inhibits RET kinase activity is being evaluated in clinical trials. Recent progress in understanding the early steps in development of papillary (PTC) and follicular (FTC) thyroid cancers also offers intriguing therapeutic opportunities.

Oncogenic Kinases in PTC

Mutations leading to constitutive activation of effectors signaling along the MAP kinase (MAPK) pathway play a central role in the pathogenesis of papillary thyroid carcinomas. A primary function of the MAPK signaling pathway is to transmit and amplify signals arising from the interaction of peptide ligands with transmembrane tyrosine kinase receptors, which, following autophosphorylation, recruit and activate a protein complex that includes RAS. This in turn initiates the sequential engagement of a series of phosphoproteins that includes RAF, MEK, and ERK, ultimately resulting in transcriptional regulation of target genes, promotion of cell cycle progression, and cell division. PTCs are associated with mutations of six different genes that code for effectors signaling along this pathway. The receptor tyrosine kinases *RET* and *NTRK* are activated through intrachromosomal inversions or translocations, leading to expression of chimeric proteins with constitutively activated tyrosine kinases.² Point mutations of *NRAS*, *HRAS*, and *KRAS* are somewhat less prevalent, and are found mostly in follicular variant PTCs.³ Finally, an activating point mutation of *BRAF* is the most common oncogenic event in sporadic PTC. The mutation is almost exclusively a thymine-to-adenine transversion at position 1799, leading to a valine-to-glutamate substitution at residue 600 (V600E).⁴ Overall, of the 916 PTCs reported to date, 42% were positive for the *BRAF*^{T1799A} mutation. The *BRAF* gene can also be activated via a novel intrachromosomal recombination in a small subset of PTCs, particularly in children with prior history of radiation exposure.⁵

A revealing feature of PTC is that the mutations in the stated genes are mutually exclusive. Several groups have examined PTCs for concordance of *RET/PTC*, *NTRK*, *BRAF*, and *RAS* mutations. Altogether, 177 PTCs have been studied, and one of these alterations was present in about 70% of tumors.⁴ However, no single PTC had a mutation in more than one of these genes. This lack of overlap provides compelling genetic evidence that a mutation of MAPK signaling components is required for transformation to PTC. These genetic events likely occur early in the course of tumor development. In addition, the disease can be recapitulated in transgenic mice

Genetic Origin of Thyroid Cancer: A Roadmap for Therapy

- Deeper knowledge of thyroid cancer pathogenesis, along with advances in medicinal chemistry and pharmacology, may help us develop selective oncoprotein inhibitors.
- Oncoproteins activated very early in thyroid cancer development are likely required for tumor maintenance, even after more genetic changes accumulate.
- Compounds that inhibit RET kinase activity hold promise for treatment of medullary thyroid cancer.
- Papillary thyroid cancers stem from mutations leading to constitutive activation of multiple effectors that signal via the MAP kinase pathway.
- Compounds that block kinase activity at distal steps in the MAP kinase pathway are logical candidate drugs for papillary thyroid cancer.

by expression of either RET/PTC or mutant BRAF in thyroid cells.⁶ Besides offering important insights into the mechanisms of thyroid cancer pathogenesis, this information is likely to guide development of future therapies. Selective kinase inhibitors acting on distal effectors of the MAP kinase pathway could be particularly well suited for PTCs that do not respond to conventional treatment.

Knowing More about FTCs

Our knowledge of the genetics of FTCs has also increased. Between 20% and 50% of FTCs harbor an interchromosomal translocation that fuses the *PAX8* gene with the *PPAR γ* gene. *PAX8/PPAR γ* is believed to act as an oncoprotein, in part through dominant-negative inhibition of the function of the wild-type copy of *PPAR γ* .^{7, 8} FTCs that do not have the *PAX8/PPAR γ* recombination are often associated with *RAS* mutations, although there is no obvious explanation for why these two distinct oncogenic steps are mutually exclusive.⁹ It is also not yet clear if these mutations occur early in tumorigenesis, although this appears likely, because both *PAX8/PPAR γ* rearrangements and *RAS* mutations are also found in a small fraction of follicular adenomas. The implications for therapy are uncertain, although there is some interest in exploring the role of *PPAR γ* ligand agonists on tumor behavior. Patients with Cowden's disease, a familial cancer syndrome, also develop benign thyroid lesions (adenomas, goiter, thyroglossal duct cyst) and FTCs.¹⁰ The gene conferring susceptibility to Cowden's disease is *P TEN*, a tumor suppressor gene whose product functions as a dual specificity phosphatase that, when inactivated by mutation, results in derepression and inappropriate activation of the phosphatidylinositol 3-kinase (PI3K)-Akt (protein kinase B) pathway. Activation of Akt/PKB has also been found in sporadic FTC and PTC, through mechanisms that are not yet known, and has been proposed to mediate tumor cell invasiveness.¹¹

Gene Expression Signatures

Advances in gene expression profiling of cancer specimens are beginning to provide experimental support for the premise that thyroid cancers with distinct oncogenes have characteristic gene expression signatures.¹² This experimental support lends further substance to the relevance of genetic changes and offers new insights into the mechanisms of cancer progression. Based on this more detailed knowledge of thyroid cancer pathogenesis and on progress in medicinal chemistry and pharmacology that allows the development of compounds that selectively inhibit specific oncoproteins, it is now reasonable to expect that patients with intractable forms of thyroid cancer could soon have access to more effective therapies.

From the Clinical Scientist:

In the past 5 years, much information has been amassed from important clinical studies done around the world, to

help guide the current best management of thyroid cancer. The more practical changes for endocrinologists include the increasing use of neck ultrasonography with color Doppler studies, which has improved practice by enhancing the diagnosis and follow-up of thyroid cancer.

The Arrival of rhTSH

Introducing recombinant human thyrotropin-alpha (rhTSH) into practice has sparked research that has steadily improved the management of patients with differentiated thyroid carcinoma. Currently approved by the Food and Drug Administration only for diagnostic use, the drug nonetheless has been successfully used in preparing patients for ¹³¹I thyroid remnant ablation, studies show, and it was recently approved in Europe for this purpose. Recent randomized prospective studies show that 30 to 50 mCi of ¹³¹I are optimal for remnant ablation.^{1, 2} Other studies show that this works when rhTSH is given in preparation for treatment.³ Although rhTSH has also been given to prepare patients for ¹³¹I treatment of distant metastases, the short half-life of ¹³¹I in cancer cells can reduce its therapeutic impact.^{4, 5} This is the most common reason for failure of ¹³¹I therapy, but it improves with lithium pretreatment or ¹³¹I dosimetry.

Serum Thyroglobulin and Ultrasonography

About 300,000 patients in the United States and 200,000 in Europe live with thyroid cancer, virtually all of whom require lifelong surveillance, so any change in follow-up paradigms would likely affect many people. It has become apparent that serum thyroglobulin (Tg) measurements made during thyroid hormone suppression of TSH are often unreliable, but by contrast, Tg stimulation by rhTSH or endogenous TSH (thyroid hormone withdrawal) provides important diagnostic information.^{6, 7} Moreover, several studies show that the role of diagnostic whole body scans (DxWBS), once the centerpiece of follow-up, has been seriously challenged, mainly on the basis of low sensitivity and high cost. DxWBS has largely been replaced by neck ultrasonography, which, in combination with Tg, has a sensitivity that approaches 100% in identifying persistent cancer. A major problem, however, is the interference caused by serum anti-Tg antibody (TgAb) in the same serum in which Tg is being meas-

New follow-up paradigms and their therapeutic dilemmas

- Recombinant human TSH in the management of thyroid cancer.
- Serum Tg in follow-up.
- Changing follow-up paradigms.
- Managing a patient with a high serum Tg and a negative whole body I-131 scan.
- The role of CT/PET studies in management.

ured. Still, TgAb can serve as a surrogate marker for Tg, falling over 2–4 years in patients with residual benign or malignant thyroid tissue that gradually disappears.⁸

Whole Body Scans and Serum Tg Levels

Novel follow-up paradigms have created new therapeutic dilemmas, not the least of which is the management of patients with high serum Tg levels and negative whole body scans. A negative post-treatment whole body scan (RxWBS) is a much different and more serious problem than a negative DxWBS. Several questions concerning this problem continue to spark debate, including what serum Tg level, if any, warrants empiric ¹³¹I therapy when the DxWBS is negative, and what effects, if any, does such therapy have on survival. Although good evidence exists that an rhTSH-stimulated Tg level > 2 ng/mL is often a marker of residual disease, this is not necessarily the cutoff that should prompt therapy. The serum Tg level that often triggers empiric ¹³¹I therapy is ~5 ng/mL after rhTSH stimulation and ~10 ng/mL after thyroid hormone withdrawal, but even use of these cutoffs must be determined according to the laboratory performing the test and the clinic administering the treatment. Also, empiric ¹³¹I treatment must be tempered by studies that show a spontaneous fall in high serum Tg levels months to years after ¹³¹I ablation without further treatment.⁷ Another study shows that serum heterophile antibodies can falsely elevate Tg results.⁹ The safest course is to observe the serum Tg over time, and to consider empiric ¹³¹I therapy when the level reaches the Tg cutoff established for a laboratory or clinic, and even then to proceed only if neck ultrasonography is negative and heterophile antibody interference is not suspected. When an ultrasonographically guided FNA identifies a malignant lymph node recurrence, neck compartment dissection is generally the preferred initial treatment, often followed by ¹³¹I therapy.

Approaches to Metastatic Disease

When patients are empirically treated with ¹³¹I, about 5%–10% have persistent tumor, depending on how they have been selected for treatment. About two-thirds have regional tumors and one-third have distant metastases—usually in the lungs. The end point in most studies of empiric ¹³¹I therapy, however, is merely a favorable change in serum Tg levels, and even this can be difficult to achieve. Empiric ¹³¹I therapy should not be given to patients with tumors known not to concentrate ¹³¹I, especially older patients with large bulky metastases.¹⁰ The best responses to empiric ¹³¹I therapy occur in children and young adults with diffuse pulmonary metastases not seen on any imaging studies except the RxWBS. A recent study of 28 children with pulmonary metastases is especially pertinent.¹¹ In this study, 32% of the children with high serum Tg levels had pulmonary metastases seen only on the RxWBS. In 2 of them, the result was positive only after two empiric ¹³¹I treatments. After an average follow-up of 103 months, 56% were free of disease, defined as a negative RxWBS and

undetectable serum Tg off levothyroxine, and 22% had a partial remission, defined as no uptake on the last RxWBS but high Tg levels (18.4 to 29.6 ng/mL). Thus empiric ¹³¹I therapy is highly effective in this setting.

¹⁸FDG-PET and CT Scanning

An important aspect of follow-up is ¹⁸F-Fluorodeoxyglucose positron emission tomographic (¹⁸FDG-PET) scanning, which is best done with simultaneous computed tomography (CT), fusing the two images together. These studies are usually done when the RxWBS is negative and the serum Tg level is high (> 10 ng/mL). Studies show that PET scanning is most accurate when rhTSH is administered before the ¹⁸FDG-PET fusion scan, which can identify tumors amenable to surgical therapy and provide important information about prognosis.¹²

From the Clinical Practitioner:

Thyroid Cancer Management

For the past 40 years, controversy in thyroid cancer has centered on the optimal extent of initial surgery and the need for radioactive iodine (RAI) ablation in low-risk patients with differentiated thyroid cancer. Fortunately, recent improvements in serum thyroglobulin (Tg) assays, the availability of recombinant human thyroid stimulating hormone (rhTSH), more widespread use of neck ultrasonography (US), and the development of fluorodeoxyglucose positron emission tomography (FDG PET) scanning has renewed the focus on issues about detecting recurrent disease in thyroid cancer survivors.¹ This is very important, because as many as 35% of patients followed for up to 40 years develop clinically evident recurrent disease.² When detected early, recurrent disease can often be effectively treated with additional surgery or radioactive iodine therapy.

Introduced to clinical medicine in the late 1940s, radioactive iodine scanning evolved into the primary modality to detect recurrent thyroid cancer.³ Unfortunately,

New Methods and Dilemmas for Detecting Recurrence

- Diagnostic RAI scanning is no longer the main tool for detecting recurrent thyroid cancer.
- Detection in low/moderate risk patients is by cervical ultrasound and serum thyroglobulin determinations.
- In low-risk patients, diagnostic whole body RAI scanning is rarely necessary in long-term follow-up monitoring for recurrence.
- FDG PET scanning can frequently identify the source of thyroglobulin in patients with non-RAI-avid metastatic lesions.
- Very sensitive detection methods detect microscopic thyroid cancer in patients thought to be disease free. But does aggressive therapy offer any clinical benefit?

only 70%–75% of metastatic lesions concentrate sufficient RAI for visualization on diagnostic scanning.³ When rhTSH became clinically available, research focused on its ability to stimulate RAI uptake for diagnostic scans.⁴ Follow-up studies demonstrated that optimal sensitivity for disease detection was achieved when the results of diagnostic scanning and TSH-stimulated thyroglobulin were considered together in individual patients.⁵ Recent retrospective studies demonstrate that up to 95% of patients with recurrent/persistent thyroid cancer will have either a positive diagnostic whole body scan or TSH-stimulated thyroglobulin of more than 2 ng/mL with either hypothyroid withdrawal or rhTSH preparation.³

New Methods for Detecting Recurrences

More recently, several authors have suggested that stimulated Tg without diagnostic whole body scanning can provide excellent sensitivity for detecting recurrent disease in low-risk patients with undetectable suppressed Tg following total thyroidectomy and RAI ablation.⁶ Along with our improved understanding of how suppressed and stimulated Tg determinations help in recurrent disease detection, neck US has also dramatically changed our approach to the detection of recurrent disease.⁷ Initially, US was considered a valuable tool for structural evaluation of the thyroid gland itself, with a secondary role in examining cervical lymph nodes. During the last 10 years, US has proven to be an invaluable tool for detecting recurrent disease in the post-operative neck that develops in residual normal thyroid tissue (after lobectomy) or in the post-operative thyroid bed or cervical lymph nodes.^{8–10}

The other major advance in detecting recurrent disease in the last 5–10 years is FDG PET scanning for detecting non-RAI-avid thyroid cancers in so-called “Tg-positive, scan-negative” patients.¹¹ Several studies now demonstrate that FDG PET scanning has a sensitivity of approximately 75% for detecting thyroid cancer that is not RAI avid. Since FDG PET scanning detects the increased glucose use by the more poorly differentiated, non-RAI-avid thyroid cancer metastases, it is not surprising that a markedly positive FDG PET scan would be associated with aggressive biologic behavior and disease-specific mortality rates greater than 50% over the 3–4 years following the scan.¹²

Thyroid Cancer Falls Chief Justice Rehnquist

Chief Justice William Hubbs Rehnquist died of thyroid cancer on September 3, 2005, at age 80. He had been diagnosed 11 months earlier and underwent a tracheostomy, external-beam radiation therapy, and chemotherapy. He worked until a couple of days before he died at his home in Virginia. His Supreme Court appointment began in 1972 and he became chief justice in 1986.

Dilemmas in Detecting Microscopic Disease

There is little question that our new paradigm for detecting recurrent disease with stimulated Tg and neck US has markedly improved our ability to detect microscopic, persistent thyroid cancer in patients we would have previously judged clinically free of disease. This increased sensitivity has naturally led to recommendations of additional treatments for these patients. The optimist sees this increased sensitivity for disease detection as an excellent opportunity for additional therapy, leading to a cure of the thyroid cancer. The pessimist worries that these sensitive tests might detect microscopic disease that will never become clinically evident, but nonetheless lead to unnecessary additional therapy with morbidities that are more clinically significant than the underlying thyroid cancer. Additional studies would help us understand the intricate balance between the need for more sensitive detection methods, the benefit of additional aggressive therapies, and the associated risks of additional treatments in patients at very low risk of dying of this disease.

Today's Standard

In 2005, sensitive Tg assays (either on suppression or with TSH stimulation) combined with neck US is rapidly becoming the standard for investigating locally recurrent disease in the long-term follow-up of most patients with differentiated thyroid cancer. FDG PET scanning tends to be reserved for patients with non-RAI-avid metastatic disease that is usually suspected based on a persistently elevated serum thyroglobulin following total thyroidectomy and RAI remnant ablation. This is causing a major paradigm shift away from the repeated use of RAI scanning as the gold standard for recurrence detection. As expected, these changing follow-up paradigms are causing as much controversy as traditional arguments about the extent of surgery and the need for RAI ablation in low-risk thyroid cancer patients. ■

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This is the seventh appearance of the tri-point perspective articles in *Endocrine News*. Past topics have been:

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