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Biologic and Clinical Perspectives on Thyroid Cancer

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Advances in the understanding of the genetic and biologic characteristics of thyroid cancer, coupled with the development of new molecular targeted therapeutics, have led to the improved diagnosis and treatment of patients with this cancer. In this review, we focus on the effect of these discoveries on all types of thyroid cancer and particularly on how they are transforming clinical care.

SPECTRUM OF THYROID CANCERS

The transformation of endodermal-derived thyroid follicular cells or neural crest–derived thyroid C cells leads to distinct types of cancer (Fig. 1). Follicular cells give rise to two main forms of differentiated thyroid cancer: papillary thyroid carcinoma and follicular thyroid carcinoma. Poorly differentiated and anaplastic thyroid carcinomas are comparatively rare tumors that also arise from follicular cells and are associated with aggressive disease. Medullary thyroid carcinoma is the canonical C-cell tumor and has distinct biologic features.

DIFFERENTIATED THYROID CARCINOMA

DIAGNOSIS

Papillary thyroid carcinoma accounts for approximately 85% of thyroid cancers. From 1975 through 2009, the incidence of thyroid cancer tripled in the United States, primarily owing to the incidental detection of small-volume papillary carcinomas on imaging studies.[1] Most papillary thyroid carcinomas are indolent clinically, consistent with their simple genome, which has few copy-number alterations. Papillary thyroid carcinoma has one of the lowest mutation densities of cancers that have been studied by means of whole-exome sequencing.[2] Although formerly thought to be a single entity, papillary thyroid carcinoma encompasses several tumor types that have mutually exclusive mutations of genes encoding effectors that signal through the mitogen-activated protein kinase (MAPK) pathway.[3,4] *BRAF* V600E accounts for 60% of these mutations, followed by *RAS* (15%) and chromosomal rearrangements that lead to illegitimate expression of the kinase domains of *BRAF* or of receptor tyrosine kinases, such as *RET*, *NTRK*, and *ALK* (12%). The remaining 13% mostly have no known driver mutations; a subgroup have copy-number abnormalities but no

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discrete recurrent genetic lesion. The different driver mutations are associated with different histologic variants of papillary thyroid carcinoma (Fig. 1) and confer distinct patterns of gene expression, signaling, and clinical characteristics.[4]

BRAF-mutated classical or tall-cell–variant papillary thyroid carcinomas have a high frequency of lymph-node metastases and recurrence after thyroidectomy; these carcinomas also have a poor response to radioiodine therapy.[5] Their refractoriness to radioiodine appears to be due to the high MAPK-pathway output that is driven by the *BRAF* V600E oncoprotein, which suppresses the expression of genes required for iodide incorporation.[6] *RAS*-mutated papillary thyroid carcinomas are associated with the follicular variant of papillary thyroid carcinoma. Follicular variant papillary carcinomas with vascular invasion spread infrequently to regional lymph nodes, retain the expression of iodine-metabolism genes, and are usually radioiodine-avid (Fig. 2).[4,7–11] Encapsulated noninvasive follicular variants of papillary thyroid carcinoma have recently been reclassified as a benign entity and renamed as "noninvasive follicular thyroid neoplasms with papillary-like nuclear features," thereby substantially reducing the number of patients who are considered to have thyroid cancer (Fig. 1).[12]

Follicular thyroid carcinomas represent 2 to 5% of thyroid cancers.[13] Follicular thyroid carcinoma and follicular variants of papillary thyroid carcinoma are associated with mutually exclusive mutations of *RAS* or of the *PAX8–PPARG* fusion oncogene.[14] The prognosis of patients with these cancers depends on the size of the tumor, the age of the patient, and the degree of angio-invasiveness, which predicts the risk of distant metastases. Hürthle-cell carcinomas, which are classified as a variant of follicular thyroid carcinoma, are genetically distinct.[15] Widely invasive Hürthle-cell carcinomas, which are characterized by extensive capsular and vascular invasion, often metastasize to lung and bone and are particularly refractory to radioiodine.

Exposure to ionizing radiation is a risk factor for the development of papillary thyroid carcinoma. After the nuclear-reactor accident in Chernobyl in 1986, there was a sharp increase in the incidence of papillary thyroid carcinomas, primarily affecting very young children in iodide-deficient regions.[16] Similar age-dependent trends were seen after the atomic-bomb explosions in Hiroshima and Nagasaki in 1945 and in persons receiving external radiotherapy for benign or malignant conditions of the head and neck. Radiation-induced papillary thyroid carcinomas have a high prevalence of fusion oncogenes, usually arising from intrachromosomal rearrangements that activate *RET* or, less frequently, the tyrosine kinase receptors encoded by *NTRK*.[17] These translocations are favored by the spatial proximity of the participating genes during inter-phase in thyroid cells, which probably predisposes them to recombination after radiation-induced DNA damage.[18] The disease-specific mortality is low, both among affected persons who have been followed for several decades and among children with sporadic papillary thyroid carcinoma.

Germline variants in chromosomes 9q22.33 and 14q13.3 are associated with a high risk of differentiated thyroid carcinoma.[19] The genes encoding FOXE1 and NKX2-1, which are master regulators of thyroid development and differentiated function, are adjacent to these loci. A total of 3 to 9% of differentiated thyroid carcinomas are familial. These may arise as

a component of cancer syndromes, such as Cowden's disease, familial adenomatous polyposis, and Werner's syndrome, which are caused by germline loss-of-function mutations in the respective genes *PTEN*, *APC*, and *WRN*. More commonly, the carcinomas occur as an isolated familial entity, defined as the presence of the disease in first-degree relatives. Recently, a germline variant of *HABP2* was shown to be associated with papillary thyroid carcinoma in an extended kindred,[20] although the validity of this finding has been questioned.[21,22]

Ultrasonography identifies lesions at high risk for cancer and is the best imaging method for the assessment of thyroid nodules. Papillary thyroid carcinomas that are less than 1 cm in the greatest dimension (papillary microcarcinomas) occur in up to 30% of adults in the general population, yet they rarely become clinically significant. Therefore, papillary microcarcinomas need not be biopsied unless there is extrathyroidal invasion, nodal metastases, or arguably, previous exposure to radiation or a family history of thyroid cancer.

Although cytopathological testing can discriminate between benign and malignant tumors, it is inconclusive in 20 to 30% of cases.[23] Two molecular diagnostic methods can sharpen the differential diagnosis. Afirma, a proprietary gene-expression classifier with a high negative predictive value, is designed to identify benign nodules among those with inconclusive results on cytopathological testing.[24,25] Alternatively, next-generation sequencing of a panel of oncogenes and tumor-suppressor genes identifies nodules with mutations that have been associated with thyroid cancer, with high positive and negative predictive values.[26] These two tests appear to reduce the incidence of unnecessary surgery, although their reliability in various clinical-practice settings remains to be established.

SURGICAL MANAGEMENT

Prospective studies of prolonged surveillance show that most papillary microcarcinomas do not progress, and surgery may be avoided or deferred in selected cases.[27] Lobectomy or total thyroidectomy is the treatment of choice for primary thyroid cancers that measure 1 to 4 cm in the greatest dimension.[28] Thyroidectomy without prophylactic central neck dissection may be appropriate for noninvasive, node-negative papillary thyroid carcinomas of tumor stage T1 (tumor size ≤2 cm in the greatest dimension; intrathyroidal) or T2 (tumor size >2 cm and ≤4 cm; intrathyroidal) and for most follicular thyroid carcinomas. Clinically involved lymph-node compartments should be resected. Total thyroidectomy with resection of involved lymph-node compartments is the recommended treatment for tumors that are larger than 4 cm in the greatest dimension.

The 10-year disease-specific mortality that is associated with differentiated thyroid carcinoma is less than 5%. The American Joint Commission on Cancer (AJCC) staging system includes prognostic variables that include the age of the patient, tumor size, invasiveness, presence and location of nodal metastases, and the presence of distant metastases. The AJCC and similar staging systems identify only a fraction of patients who are at risk for death, probably because of failure to incorporate variables such as histologic characteristics, functional status (e.g., radioiodine avidity or positivity on ^{18}F-fluorodeoxyglucose–positron-emission tomography [FDG-PET]) of distant metastases, key molecular markers, and initial response to therapy. Also, the AJCC classification does not

predict the risk of recurrence, which is problematic because the method and intensity of surveillance and therapy are guided by individualized estimates of the risk of recurrence. Dynamic stratification of patients with differentiated thyroid carcinoma according to their response to initial therapy improves the prediction of the risk of recurrent or persistent disease as well as disease-specific mortality.[29]

Recent guidelines propose a more comprehensive set of variables to identify patients who are at low, intermediate, or high risk for recurrence.[28] Among these variables, molecular markers show promise. Most groups have shown that the *BRAF* V600E mutation alone is of no practical value in risk stratification, even though it is associated with a greater likelihood of nodal recurrence than papillary cancers driven by other oncogenes.[30] Somatic mutations of the telomerase gene (*TERT*) promoter are present in approximately 9% of papillary thyroid carcinomas.[4,15,31,32] These mutations generate de novo binding motifs for the ETS (also called E26) family of transcription factors, resulting in inappropriate activation of telomerase expression.[33] Such expression presumably leads to immortalization, a high likelihood of additional oncogenic events, and disease progression. Among patients with papillary thyroid carcinomas with both the *BRAF* V600E and *TERT* mutations, progression-free survival is markedly shorter than among those with *BRAF* V600E mutations alone.[34] However, the risks and benefits of initiating intensive therapies that are based solely on genetic profiling need to be understood before their introduction into clinical practice.

RADIOIODINE THERAPY

Radioiodine therapy leverages the property of thyroid follicular cells to transport and incorporate iodide into thyroglobulin, a feature that is retained in a subgroup of differentiated thyroid carcinomas. Until recently, most patients with differentiated thyroid carcinoma received postoperative radioiodine therapy despite a lack of data from prospective clinical trials to support the practice. Radioiodine therapy is no longer recommended in patients with low-risk thyroid cancers, because the recurrence rate and mortality are low and large retrospective series have not shown improved outcomes.[35,36] The data regarding radioiodine therapy in patients with intermediate-risk disease are not compelling; however, the treatment may be useful in a subgroup of patients who have high levels of thyroglobulin after surgery and persistent structural disease. Postoperative therapy with either 30 or 100 mCi (1.1 or 3.7 GBq) of iodine-131 is equally effective in ablating the remnant thyroid, regardless of whether injections of recombinant human thyrotropin or thyroid-hormone withdrawal is used to induce iodide accumulation.[37]

BRAF-mutated cancers and those that are positive on FDG-PET scans are often refractory to radioiodine.[38] The expression of genes that are required for iodine transport and metabolism is low in most *BRAF*-mutated cancers, whereas they are comparatively preserved in *RAS*-mutated papillary thyroid carcinomas (Fig. 2).[4] Accordingly, *Braf* V600E suppresses the expression of these genes in mouse models of papillary thyroid carcinoma and inhibits radioiodine uptake and response to radioiodine therapy, which can be partially restored by treatment with rapidly accelerating fibrosarcoma (RAF) or MAPK kinase (MEK) inhibitors.[6] A pilot trial of the MEK inhibitor selumetinib in patients with radioiodine-refractory metastatic thyroid cancer showed the restoration of iodide uptake at metastatic

sites in 14 of 20 patients. In 8 of the 14 patients, the uptake was sufficient to enable iodine-131 therapy with remarkable clinical responses (Fig. 2).[11] Similar results have been shown with the BRAF inhibitor dabrafenib.[39] An ongoing phase 3, placebo-controlled, double-blind, randomized trial (ClinicalTrials.gov number, NCT01843062) is evaluating the ability of selumetinib to enhance the response to adjuvant radioiodine therapy in patients at high risk for locoregional recurrence.

Most patients with differentiated thyroid carcinoma are treated with high doses of thyroid hormone, which are sufficient to suppress the secretion of thyrotropin. The intensity and duration of suppressive therapy can be affected by disease status. It is unclear whether this therapy benefits patients with *BRAF*-mutated papillary thyroid carcinoma, because most such tumors express low levels of the thyrotropin receptor.[4]

Patients with low-risk or intermediate-risk disease are followed by means of neck ultrasonography and measurements of serum thyroglobulin levels. Antithyroglobulin antibodies, which are present in patients with autoimmune thyroiditis, can interfere with the accuracy of thyroglobulin immunoassays; however, persistent or rising levels of antithyroglobulin antibody also indicate disease activity. Diagnostic radioiodine scans have low sensitivity and are unhelpful in routine surveillance unless there is structural or biochemical evidence of disease. Additional imaging studies, including FDG-PET scans, may help localize disease in patients with rising levels of thyroglobulin or antithyroglobulin antibody. Clinically apparent persistent or recurrent cervical nodal disease is found in approximately 10% of patients with thyroid cancer. Selected cases can be managed expectantly or by means of surgical resection, thermal destruction, or alcohol ablation.[40–42]

SYSTEMIC THERAPIES FOR METASTATIC RADIOIODINE-REFRACTORY THYROID CANCER

Thyroid cancers are often indolent, even when they have metastasized to distant sites. Most physicians reserve systemic therapy for patients who have metastatic disease that is progressing, symptomatic, or in a location that threatens vital structures and is not amenable to localized therapies. Palliative radiotherapy, either alone or concomitant with low-dose chemotherapy, or local therapies may control disease in patients with unresectable regional or metastatic disease.[40,41,43] Treatment with bisphosphonates or anti–receptor activator of nuclear factor-κB (RANK) ligand antibody may benefit patients who have bone metastases, although the efficacy of the compounds has not been tested in prospective trials.[44]

The Food and Drug Administration (FDA) approved two multikinase inhibitors, sorafenib and lenvatinib, for the treatment of patients with radioiodine-refractory metastatic thyroid cancer on the basis of phase 3, prospective, double-blind, randomized, placebo-controlled trials that showed longer progression-free survival (Table 1).[45,46] Although the two drugs have not been compared with each other, lenvatinib appears to have greater efficacy than sorafenib.[49] Adverse effects of the two drugs make the maintenance of full-dose therapy a challenge. The effects of the drugs on quality of life and the long-term cumulative toxic effects remain to be fully explored.

Phase 2 trials of other multikinase inhibitors that target vascular endothelial growth factor (VEGF) receptor signaling have shown efficacy in this disease.[50–52] The mechanisms of action of these drugs are unknown, primarily because they inhibit multiple oncologic targets. Thyroid cells require contact with capillaries to function normally and secrete trophic signals for capillary endothelial cells, primarily VEGF.[53] On transformation and loss of polarity, a disorganized tumor vasculature may result in cancer-cell hypoxia, loss of immune surveillance, increased VEGF-receptor activation, and a dependence on VEGF-receptor signaling that can be leveraged therapeutically.[54] Sorafenib and lenvatinib are thought to act by suppressing angiogenesis, because they inhibit VEGF receptors 1, 2, and 3. They also have distinct activity profiles against other kinases. Consequently, the therapeutic window with which they inhibit their respective targets affects clinical outcomes in ways that are poorly understood.

Advanced thyroid cancers also have cell-autonomous oncogenic defects that generate vulnerabilities that can be exploited therapeutically.[15] Chief among them is the *BRAF* V600E mutation, which is the most common driver along the entire spectrum of the disease.[55] *BRAF* confers susceptibility to selective RAF kinase inhibitors in some, but not all, cancer lineages. Thus, patients with *BRAF*-mutated melanoma or hairy-cell leukemia have a high response rate to vemurafenib,[56,57] whereas patients with colorectal cancer do not.[58] The low sensitivity of colorectal cancer cells to growth inhibition by vemurafenib is due in part to the activation of epidermal growth factor receptor signaling.[59,60] An analogous mode of adaptive resistance is also seen in cell lines of *BRAF*-mutated thyroid cancer and murine Braf-induced papillary thyroid carcinomas, which are refractory to vemurafenib by means of the activation of human epidermal growth factor receptor 3 (HER3) signaling. Accordingly, the response rate among patients with *BRAF*-mutated papillary thyroid carcinoma in a phase 2 trial of vemurafenib was 38.5%, which is considerably less than among patients with melanoma.[61]

Combination trials with RAF and MEK inhibitors, as well as RAF and HER3 inhibitors, are currently in development. Some advanced thyroid cancers have rearrangements of *ALK*, *RET*, *NTRK1*, *NTRK3*, or *FGFR*, which can be targeted by selective kinase inhibitors with proven efficacy in other tumor types. Because the prevalence of these mutations is low among thyroid cancers, patients can be enrolled in “basket trials,” in which the efficacy of a drug targeting a particular molecular abnormality is studied in cancers of different lineages.

Hence, the biologic underpinnings of meta-static, differentiated thyroid cancers offer two potential strategies for systemic treatment: disrupting the disorganized tumor vasculature and blocking the primary oncogenic driver. The ultimate application of these two approaches, either sequentially or in combination, remains to be defined but offers much promise.

POORLY DIFFERENTIATED AND ANAPLASTIC THYROID CARCINOMAS

Poorly differentiated thyroid carcinomas are aggressive and are defined histologically by a combination of architectural and high-grade features (high mitotic rate and presence of necrosis).[62,63] Poorly differentiated thyroid carcinomas represent approximately 6% of

thyroid cancers and are associated with a mean survival of 3.2 years. Radioiodine therapy is of limited benefit. Most patients require systemic therapies that are similar to those described for differentiated thyroid carcinomas.

Anaplastic thyroid carcinomas account for approximately 1% of thyroid cancers and are associated with a mean survival of 6 months. They are refractory to radioiodine, and traditional chemotherapy and radiotherapy are of limited benefit.[64] Anaplastic thyroid carcinomas probably arise from preexisting differentiated or poorly differentiated thyroid carcinomas (Fig. 3) and have a high mutation burden.[4,55] Although *BRAF* and *RAS* are the predominant drivers, anaplastic thyroid carcinomas are characterized by frequent mutations in *TP53*, the *TERT* promoter, effectors of the phosphatidylinositol 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) pathway, and genes involved in epigenetic regulation, including components of the SWI/SNF complex and histone methyltransferases (Fig. 3).[55] Mutations in *EIF1AX*, a component of the translational preinitiation complex, are markedly enriched in poorly differentiated and anaplastic thyroid carcinomas and have a striking pattern of co-occurrence with *RAS*.

The genetic complexity of anaplastic thyroid carcinomas underscores their extreme virulence. When possible, these tumors should be resected and the patient treated with locoregional radiation therapy and chemotherapy with taxanes, either alone or in combination with carboplatin or doxorubicin.[65] In patients with unresectable disease, preservation of the airway is critical, and palliative therapy is often the only option. Despite their genomic complexity, some anaplastic thyroid carcinomas retain dependence on the genetic drivers,[66,67] and it is important to consider enrollment in experimental trials early in the course of disease. Candid discussions with patients and families about the extent and intensity of medical interventions and the option of home or institutional hospice care are important aspects of treatment.

MEDULLARY THYROID CARCINOMA

PATHOGENESIS

Medullary thyroid carcinoma accounts for 3 to 5% of thyroid cancers. In 75% of patients, the medullary thyroid carcinoma is sporadic, usually developing in the fourth to sixth decade of life. Less often, medullary thyroid carcinoma is the dominant component of the hereditary multiple endocrine neoplasia (MEN) type 2 syndromes, MEN2A and MEN2B (Table 2).[68–77] MEN2A accounts for 95% of the cases of MEN type 2 and has four variants: classical MEN2A, MEN2A with Hirschsprung's disease, MEN2A with cutaneous lichen amyloidosis, and isolated familial medullary thyroid carcinoma. MEN2B is characterized by a typical physical appearance and associated abnormalities.

RET, a gene encoding a receptor tyrosine kinase, is the dominant oncogene in medullary thyroid carcinoma. More than 100 gain-of-function *RET* mutations have been reported in patients with medullary thyroid carcinoma, including germline mutations in patients with hereditary disease and somatic mutations in patients with sporadic disease (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[78] There is a correlation between genotype and phenotype in hereditary medullary thyroid carcinoma.

Thus, patients with MEN2A or MEN2B have multicentric disease, and other endocrine tumors or associated abnormalities may develop, depending on the specific *RET* mutation (Table 2). Somatic *RET* mutations are the most common drivers in sporadic medullary thyroid carcinoma, followed by *RAS* mutations and *RET* or *ALK* fusions.[68–70] The clinical aggressiveness of hereditary or sporadic medullary thyroid carcinoma is related to the *RET* mutation.

Screening for *RET* germline mutations by direct DNA analysis is important in family members who are at risk for hereditary medullary thyroid carcinoma. Such screening is also important in patients with presumed sporadic medullary thyroid carcinoma, because approximately 7% of them will be found to have MEN2A.[79] Medullary thyroid carcinoma cells secrete calcitonin and carcinoembryonic antigen (CEA). Serum levels of these markers are directly related to the parafollicular or C-cell mass and are useful in screening family members who are at risk for medullary thyroid carcinoma, in detecting persistent or recurrent medullary thyroid carcinoma after thyroidectomy, and in monitoring the response to local or systemic therapy.

DIAGNOSIS

Ultrasonography and cytologic testing of thyroid nodules by means of fine-needle aspiration are the preferred tests for the diagnosis of medullary thyroid carcinoma. If cytopathological testing is inconclusive, immunohistochemical testing for calcitonin in aspirated cells or the measurement of calcitonin in the washout fluid of the fine-needle aspiration may be diagnostic.[80] Many centers in Europe measure serum calcitonin levels in all patients with thyroid nodules, and medullary thyroid carcinoma is detected in approximately 0.4% of them. However, this practice is controversial and has not been widely adopted.[81,82]

SURGICA MANAGEMENT

Surgery is the primary treatment for patients with sporadic or hereditary medullary thyroid carcinoma and ranges from thyroid lobectomy (in selected patients with sporadic disease), to total thyroidectomy with or without central neck dissection, to total thyroidectomy with central neck dissection and unilateral or bilateral lymph-node–compartment dissection. The type of operation depends on the age of the patient and the extent of disease as determined by means of physical examination, imaging of the neck, and measurement of serum calcitonin levels.[78,83] In families with MEN2A or MEN2B, prophylactic thyroidectomy is indicated in clinically normal children who inherit a mutated *RET* allele. The age of onset depends to some extent on the specific *RET* mutation; however, given a specific *RET* mutation, the age of onset varies among and even within families.

In patients who have inherited a mutated *RET* allele, the reliable indicator for timing thyroidectomy is the serum calcitonin level rather than the specific *RET* mutation. The risk of nodal metastases is low among children younger than 10 years of age, and residual medullary thyroid carcinoma after thyroidectomy is uncommon in children younger than 8 years of age.[84] Therefore, most children younger than 8 years of age can be treated by total thyroidectomy, without central neck dissection, which reduces the incidence of hypoparathyroidism. Medullary thyroid carcinoma is highly aggressive in MEN2B, and

thyroidectomy should be performed when the diagnosis is made, even in the first year of life. In all patients with hereditary medullary thyroid carcinoma, it is imperative that the presence of a pheochromocytoma be ruled out before thyroidectomy.

After thyroidectomy, patients are evaluated at 6-month to yearly intervals by means of physical examination and measurement of serum calcitonin levels. An undetectable serum calcitonin level indicates the absence of C cells, whereas a detectable level, even in the normal range, indicates the presence of residual C cells in a thyroid remnant or at a locoregional or distant site, or the presence of a nonthyroid cancer that is secreting calcitonin.[85] If the serum calcitonin level remains undetectable for 5 years after surgery, the patient is probably cured; however, patients with a measurable calcitonin level may remain asymptomatic for many years without clinical evidence of recurrence.

The most accurate measure of the aggressiveness of medullary thyroid carcinoma is the doubling time for levels of serum calcitonin or CEA. The prognosis of patients with an elevated level of serum calcitonin or CEA is directly related to the time it takes for the marker to double. Doubling times that are less than 6 months are especially ominous, whereas those that are greater than 2 years are associated with long-term survival.[78]

SYSTEMIC THERAPY

Although many patients with metastatic medullary thyroid carcinoma can be followed expectantly, it is important to treat those who have progressive or symptomatic disease with systemic therapy. Standard chemotherapy is characterized by low rates of response of short duration and is seldom used as the initial treatment. The FDA approved the multikinase inhibitors vandetanib and cabozantinib on the basis of prolongation of progression-free survival, as compared with placebo, in separate, randomized, phase 3 clinical trials involving patients with advanced medullary thyroid carcinoma (Table 1).[47,48] The responses were partial, and although some were durable, progressive disease developed in the majority of patients. No survival advantage has been shown with either drug. Also, the drugs are costly and are associated with toxic effects, often leading to dose reduction or termination of treatment.

As with sorafenib and lenvatinib, the mechanisms of action of vandetanib and cabozantinib are unclear. The lack of specificity for RET diminishes their therapeutic window, because the inhibition of other kinases results in toxic effects at high doses. Current evidence indicates that the kinase activity of oncogenic drivers must be inhibited profoundly for maximal therapeutic benefit.[86] Accordingly, there is growing interest in developing more selective *RET* kinase inhibitors, which may be more effective in patients with medullary thyroid carcinomas or other cancers that are driven by *RET* fusions, such as non–small-cell lung cancer,[87] papillary thyroid carcinoma, and myelomonocytic leukemia.[88]

SUMMARY

Recent discoveries in molecular medicine, coupled with advances in biotechnology and medicinal chemistry, have led to enormous progress in the diagnosis and treatment of patients with thyroid cancer. We have no doubt that this progress will continue with the

development of more effective therapies that are based on new compounds with greater specificity for oncogenic targets and combinatorial regimens that overcome resistance to single agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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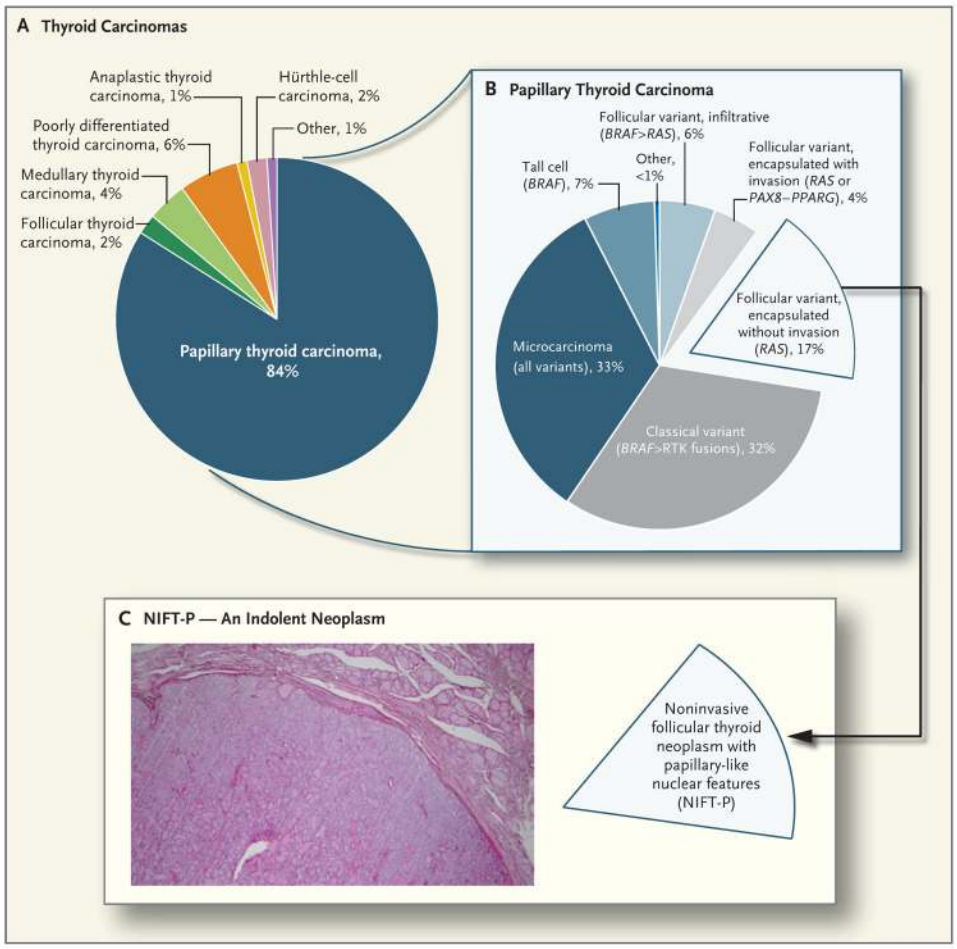

Figure 1. Pathologic Spectrum of Thyroid Cancers

Panel A shows the relative incidence of the main types of thyroid cancer in the United States, and Panel B the relative frequency of pathologic variants of papillary thyroid carcinoma, with their corresponding main driver mutations shown in parentheses (the symbol > indicates more frequent than). RTK denotes receptor tyrosine kinase. Panel C shows the encapsulated follicular variant of papillary thyroid carcinoma without invasion, which until recently represented 17% of all papillary thyroid carcinomas. This cancer has recently been reclassified as a neoplasm of low malignant potential and is now termed "noninvasive follicular thyroid neoplasm with papillary–like nuclear features" (NIFT–P). This change will result in a corresponding reduction in the number of patients who are considered to have thyroid cancer. The hematoxylin and eosin–stained section in the inset shows the characteristic histologic appearance of an NIFT–P. The encapsulated tumor has a follicular growth pattern and papillary nuclear features, low mitotic rate, and absence of necrosis and capsular or vascular invasion.

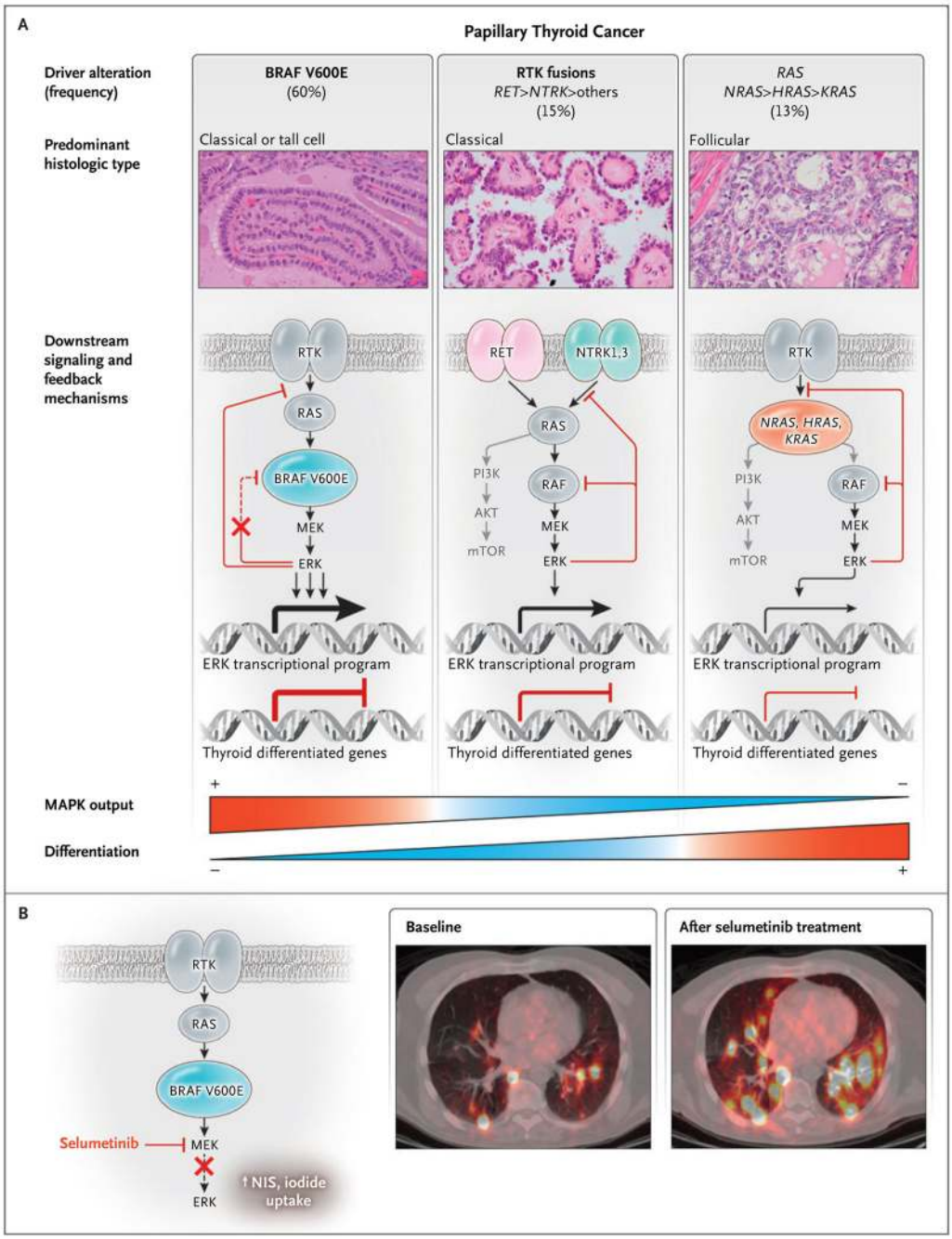

Figure 2. Functional Consequences of Driver Mutations in Papillary Thyroid Carcinomas

Panel A shows that papillary thyroid carcinomas have mutually exclusive activating mutations in *BRAF*, *RAS*, and RTK. The photomicrographs show hematoxylin and eosin–stained slides of the indicated variants of papillary thyroid carcinoma. Mutant RTKs, *RAS*, and *BRAF* activate mitogen–activated protein kinase (MAPK) signaling but do so to different degrees. The symbol > indicates more frequent than. The signaling output driven by *BRAF* V600E is highest, because this oncoprotein signals as a monomer and is unresponsive to the negative–feedback effects of activated ERK on upstream inputs into the

pathway.[7–9] By contrast, the MAPK–signaling flux that is evoked by fusion RTK proteins or by mutated *RAS* is dampened by negative feedback. The expression of genes that is required for iodide uptake and metabolism, which are hallmarks of the differentiated state of thyroid follicular cells, is inhibited by MAPK signaling. This is consequential, because responsiveness to radioiodine therapy requires preservation of thyroid–differentiated function. The weight of the lines and arrows indicates the magnitude of the flux through the MAPK pathway and the transcriptional activities, respectively. The term mTOR denotes mammalian target of rapamycin, and PI3K phosphatidylinositol 3–kinase. Panel B (left side) shows that the MAPK kinase (MEK) inhibitor selumetinib decreases extracellular signal –regulated kinase (ERK) activation and restores expression of the sodium iodide transporter (NIS) and other thyroid differentiation genes in mice with *Braf* V600E–driven papillary thyroid carcinoma.[6] The insets on the right side of Panel B are fused iodine–124 positron –emission tomographic–computed tomographic images showing the restoration of iodine –124 uptake with selumetinib treatment in a patient with radioiodine–refractory lung metastases of thyroid cancer. Adapted, with permission, from Ho et al.[11]

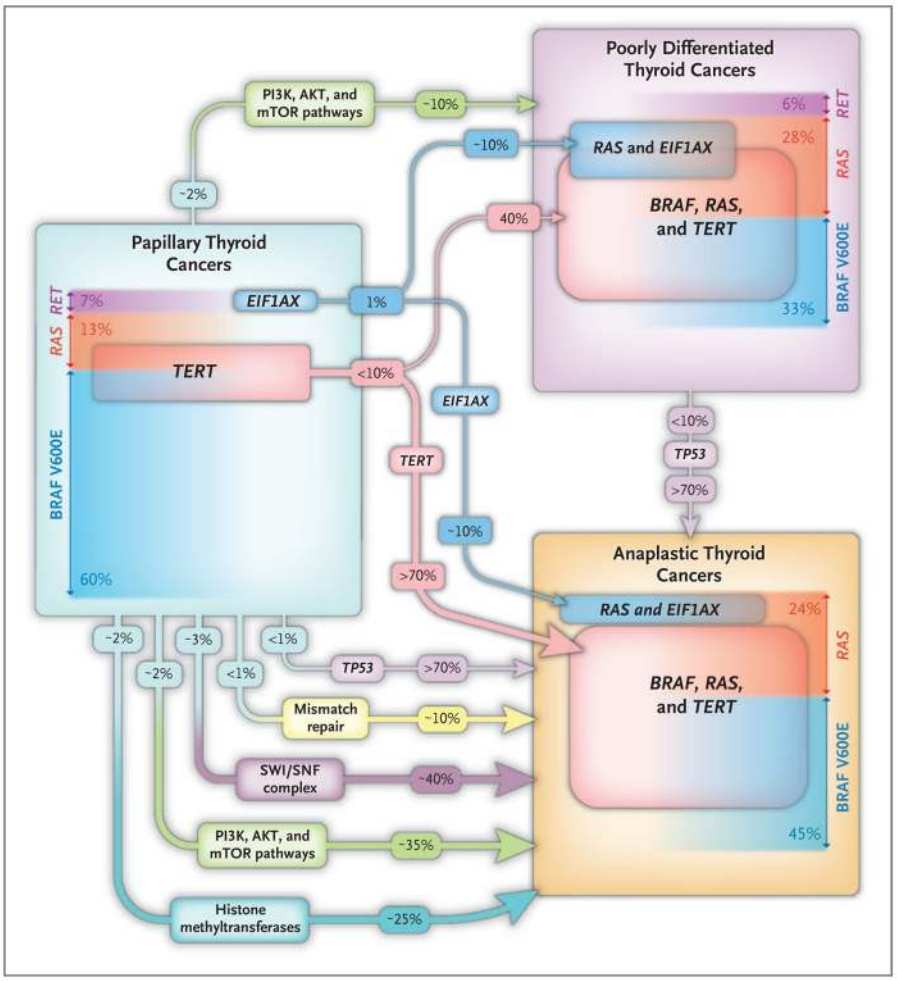

Figure 3. Genomic Hallmarks of Thyroid Cancer along the Spectrum of Disease Progression

The frequency of the main somatic genetic defects in papillary, poorly differentiated, and anaplastic thyroid carcinoma is shown, based on the largest published series studied by next–generation sequencing.[4,55] Because anaplastic thyroid carcinomas are extensively infiltrated by tumor–associated macrophages, deep sequencing is required to make reliable mutation calls. The prevalence of driver mutations (*BRAF*, *RAS*, and *RET*) in the histologic types of the three tumors is shown. In patients with advanced disease, tumors may have more than one mutation, so the overall mutation burden exceeds 100%. The frequency of the main drivers (*BRAF*, *RAS*, and *RET*) sums to less than 100% because in some cases the drivers are not known or they are lower–frequency events and are not listed here (e.g., *NF1*, *PTEN*). *TERT* promoter mutations appear to be key transitional steps in the microevolution of tumors. In papillary thyroid carcinoma, the *TERT* mutations are infrequent (in 10% of tumors) and usually subclonal. By contrast, their prevalence is substantially higher in poorly differentiated and anaplastic thyroid carcinomas, in which they are uniformly clonal. Mutations in *TP53* are infrequent in all histologic types of thyroid cancer with the exception of anaplastic thyroid carcinomas, in which they occur in more than 70% of patients. Anaplastic thyroid carcinomas have mutations in genes encoding components of the PI3K–AKT–mTOR pathway and of proteins involved in epigenetic regulation, whereas poorly

differentiated thyroid carcinomas have an intermediate frequency of these events (data not shown). Mutations of *EIF1AX*, a component of the translation preinitiation complex, are infrequent and are mutually exclusive with other driver mutations in papillary thyroid cancer. In poorly differentiated and anaplastic thyroid cancers, they are markedly enriched and are strongly associated with *RAS*–mutated tumors.

Table 1

Phase 3 Clinical Trials of Kinase Inhibitors in Patients with Differentiated or Medullary Thyroid Carcinoma.*

Drug and Trial	No. of Patients		Tumor	Progression-free Survival				Dose-Related Events in Active-Drug Group	Deaths in Active-Drug Group
	Active Drug	Placebo		Active Drug	Placebo	Hazard Ratio (95% CI) †	P Value		
				mo				*% of patients*	*no.*
Sorafenib (DECISION)[45]	207	210	DTC	10.8	5.8	0.59 (0.45–0.76)	<0.001	64 had dose reduced, and 18 discontinued	12, with 1 considered to be drug related
Lenvatinib (SELECT)[46]	261	131	DTC	18.3	3.6	0.21 (0.14–0.31)	<0.001	68 had dose reduced, and 14 discontinued	20, with 6 considered to be drug related
Vandetanib (ZETA)[47]	231	100	MTC	30.5	19.3	0.46 (0.31–0.69)	<0.001	35 had dose reduced, and 12 discontinued	5, with 1 considered to be drug related
Cabozantinib (EXAM)[48]	219	111	MTC	11.2	4.0	0.28 (0.19–0.40)	<0.001	79 had dose reduced, and 22 discontinued	12, with 9 considered to be drug related

*DECISION was a multicenter, randomized, double–blind, placebo–controlled phase 3 trial of sorafenib in patients with radioactive iodine–refractory locally advanced or metastatic, progressive, differentiated thyroid cancer,[45] SELECT a phase 3, randomized, double–blind, multicenter trial of lenvatinib, as compared with placebo, in patients with progressive differentiated thyroid cancer that is refractory to iodine–131,[46] ZETA a phase 3 prospective, randomized, double–blind, trial of vandetanib, as compared with placebo, in patients with locally advanced or metastatic medullary thyroid cancer,[47] and EXAM a phase 3 prospective, randomized, double–blind, trial of cabozantinib, as compared with placebo, in patients with progressive advanced medullary thyroid cancer.[48] Progression–free survival was the primary end point in each of the four trials. Outcome comparisons of these trials should be done with caution because there were differences in trial design and eligibility criteria. CI denotes confidence interval, DTC differentiated thyroid carcinoma, and MTC medullary thyroid carcinoma.

†The hazard ratio is for disease progression or death. A 99% confidence interval was used for the hazard ratio in the SELECT trial.[46]

Table 2

Characteristics of Sporadic Medullary Thyroid Carcinoma, MEN2A, and MEN2B.*

Disease	Associated_Phenotype	Mutations.†	Clinical_Characteristics
Sporadic MTC	None	*RET* (in approximately 50%), *HRAS*, *NRAS*, or *KRAS* (in 0 to 43%)[68]; rarely mutations in *KIT* or *MET* or fusions of *RET* or *ALK*[69,70]	*RET* M918T associated with more aggressive MTC than *RAS*[71]
MEN2A			
Classical	Pheochromocytoma (in 20 to 50%) and hyperparathyroidism (in 12 to 30%)	95% of *RET* mutations occur in exon 10 (codon 609, 611, 618, or 620) or exon 11 (codon 634)	Pheochromocytoma occurs in 30 to 50% of patients with *RET* mutations in exon 11[72] and in 15% of those with *RET* mutations in exon 10; hyperparathyroidism occurs in 30% of patients with *RET* mutations in exon 11 and in <12% of those with *RET* mutations in exons other than 11[73]
With Hirschsprung's disease	Hirschsprung's disease	*RET* mutation in exon 10 at codon 620 (in 50%) and less often at codon 618, 609, or 611[74]	MEN2A in 2 to 5% of patients with Hirschsprung's disease[75]
With cutaneous lichen amyloidosis	Cutaneous lichen amyloidosis	Usually *RET* mutation in codon 634[76]	In approximately 30% of patients with MEN2A; may precede onset of medullary thyroid carcinoma[76]
Familial MTC	None	Broad range of *RET* mutations	Appears to be less aggressive than the MTC associated with classical MEN2A
MEN2B	Typical facies, marfanoid habitus, medullated corneal nerves, and aerodigestive tract ganglioneuromatosis	*RET* M918T mutations in more than 95%, and *RET* A833F in the remainder	*RET* M918T associated with more aggressive MTC than *RET* A833F[77]

*MEN2A denotes multiple endocrine neoplasia type 2A, and MEN2B multiple endocrine neoplasia type 2B.

†Patients with sporadic MTC have somatic *RET* mutations, whereas patients with MEN2A or MEN2B have germline *RET* mutations.