Thyroid Cancer: Risk-Stratified Management and Individualized Therapy

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Abstract

Thyroid cancer is the most common endocrine malignancy. Differentiated thyroid cancer (DTC) with the two subtypes, papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), is the most frequent subtype of thyroid cancer; more rare subtypes are medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC). The incidence of DTC has increased rapidly in recent years due to the more frequent use of imaging methods such as ultrasound of the neck and fine-needle aspiration (FNA) of thyroid nodules. After total thyroidectomy and radioiodine treatment, DTC remains an indolent and curable disease in most patients, whereas the cure rate in MTC is lower and depends on early diagnosis. Most ATCs are incurable. In recent years, there has been great progress in identifying genetic changes in thyroid cancer, and genetic testing of FNA samples or blood samples provides useful information for clinical decision making. Tumor staging, either postoperatively or by imaging, and measuring the tumor markers thyroglobulin for DTC and calcitonin for MTC, allow for dynamic risk-adapted stratification for follow-up procedures. In advanced metastatic thyroid cancer, molecular targeted therapy using tyrosine kinase receptor inhibitors, including sorafenib, lenvantinib, vandetanib, and cabozantinib, helps control tumor progression and prolongs progression-free survival. Using a dynamic risk-stratified approach to manage thyroid cancer, the outcomes for most thyroid cancer patients are excellent compared with those for other cancers. The major challenge in the future is to identify high-risk patients and to treat and monitor them appropriately. *Clin Cancer Res; 22(20); 5012–21. ©2016 AACR.*

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Introduction

In the past three decades, the number of people diagnosed with thyroid cancer worldwide has increased dramatically (1–4). In 2011, there were more than 500,000 people with thyroid cancer in the United States, and it is projected that in 2016, there will be more than 64,000 new cases and more than 1,980 thyroid cancer–associated deaths in the United States (5). The yearly incidence of thyroid cancer has risen over the past 40 years from 4.9 per 100,000 in 1975 to 14.3 per 100,000 in 2009 (6), but the age- and sex-adjusted annual death rate of 0.5 per 100,000 has remained stable (7). The increased incidence is due almost entirely to an increase in the incidence of papillary thyroid cancer (PTC; ref. 8); in turn, the PTC increase is due mainly to the increasing use of neck ultrasonography (U.S.), to the improved feasibility of performing US-guided fine-needle aspiration (FNA) biopsy of very small nodules, to the increase in thyroid surgery that reveals occult cancers, and to better histologic analysis of surgical specimens (9, 10). The increased incidence is much more pronounced for small indolent cancers (<2 cm in diameter; ref. 11). In industrialized countries, around 40% of all treated thyroid carcinomas are microcarcinomas (<1 cm in diameter) with excellent long-term prognoses (12), which is in line with autopsy findings that occult papillary thyroid microcarcinomas are present in 4% to 36% of cases (a mean prevalence of 11.5%; ref. 13). The incidence of other types of thyroid cancer, including follicular thryoid cancer (FTC) and medullary thyroid cancer (MTC), and aggressive subtypes such as poorly differentiated follicular and anaplastic carcinomas (ATC), has probably not increased. The survival rates of patients affected by thyroid cancer are highly variable and depend on the histotype and the degree of differentiation. Rates are 95% and 80% after 35 to 40 years for PTC and FTC, respectively; 65% for MTC after 10 years; less than 20% for poorly differentiated thyroid cancer (DTC) at 5 years; and less than 10% for ATC at 6 months after the initial diagnosis (14).

These trends should be considered when deciding upon the initial treatment and follow-up protocol for patients with thyroid cancer. One major goal is to minimize the potential harm from overtreatment in the majority of patients who are at low risk of disease-specific mortality and morbidity while appropriately treating and monitoring patients who are at higher risk. These changes and the need for new risk-stratified approaches for patients with thyroid cancer have recently prompted new guidelines in many countries (15–22).

Thyroid Nodules and Risk-Stratified Diagnostics: Case Findings

Thyroid nodules, which are mostly benign, are very common in the general population. Most are diagnosed as unexpected asymptomatic thyroid tumors that are discovered while investigating unrelated conditions (12, 23). There is a female preponderance and an increase in prevalence with age, reaching 30% to 40% in individuals more than 50 years old. The prevalence of thyroid nodules increases with advancing age, while the risk that such nodules are malignant decreases.

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Nonetheless, when thyroid cancer is detected in older individuals, a higher risk histologic phenotype is more likely. Older patients are more likely to have higher risk PTC variants, poorly differentiated cancer, or ATC (24).

All patients with a thyroid nodule, regardless of the mode of detection, should undergo a dedicated neck US for quantitative risk stratification. Microcalcifications, irregular margins, and a taller-than-wide shape are the features with the highest specificities (>70%–90%) for thyroid cancer, although the sensitivities are significantly lower for any single feature (25, 26). Notably, no single US feature and no single US feature combination is sensitive or specific enough to identify malignancy (27). However, thyroid US is widely used to stratify the risk of malignancy for thyroid nodules and to aid in decision making about whether FNA is indicated.

Diagnostic FNA should be performed on nodules >1 cm with a suspicious US pattern. Thyroid nodule FNA cytology should be reported using the diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology, which has six diagnostic categories that range from nondiagnostic to malignant (28, 29). Surgery is generally recommended if the cytology results suggest primary thyroid malignancy. For thyroid nodules that are classified as indeterminate on FNA biopsy, molecular testing can be used to determine whether a nodule is likely to be benign or malignant (30).

Molecular Genetics and Diagnosis of Thyroid Cancer

Considerable progress has been made in understanding the molecular mechanisms of thyroid cancer in the past 20 years (Fig. 1). Common driver abnormalities in PTC responsible for initiation of thyroid cancer development center around constitutive activation of the MAPK cellular signaling pathway through mutational activation of *BRAF*, *NRAS*, and gene rearrangements, including those involving the tyrosine kinase Ret (*RET/PTC*; refs. 31–33). FTC is frequently linked to activation of the PI3K and MAPK pathways, through loss of PTEN expression, *NRAS* mutations, rearrangements such as *PPARγ/PAX8*, and other events (31, 32). ATCs are more genomically complex, frequently harboring multiple abnormalities including genes encoding tyrosine kinase receptors (TKR)—such as *VEGFR*, *MET*, *EGFR*, *PDGFR*, *KIT*, and *PI3K/AKT* pathway kinases, including *PIK3CA*, *PIK3CB*, 3 phosphoinositide–dependent protein kinase 1 (*PDPK1*)—and increased expression of stem cell markers (34). Finally, MTC, a neoplasm arising from the C cells, is caused most frequently by either germline (familial MTC or multiple endocrine neoplasia type 2A) or somatic activating mutations in *RET* or *RAS* genes (35–37). *RAS* mutations did not overlap with mutations in *RET* in sporadic MTC, which indicates that each type of mutation is an alternative driver event for MTC (38). Despite the many genetic

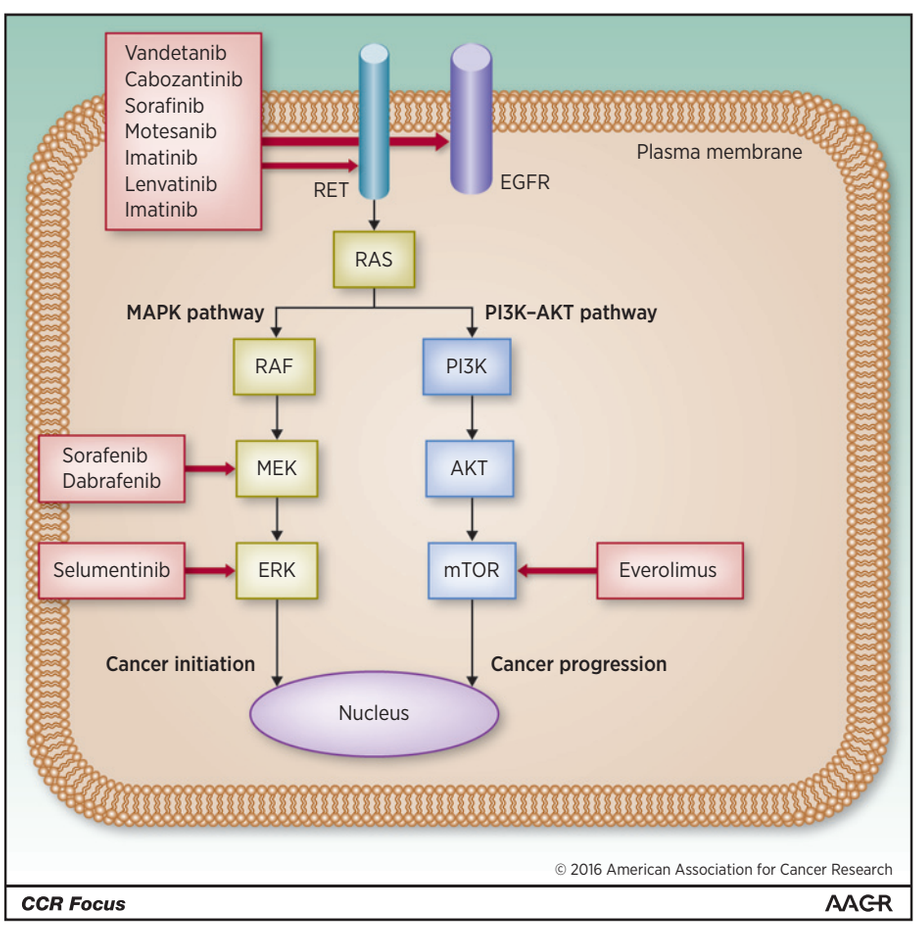

Figure 1.
Signaling pathways implicated in thyroid carcinogenesis and possible targets for therapeutic interventions. The two pathways (RAS/RAF/MEK/ERK and PI3K/AKT/mTOR) are involved in the propagation of signals from the cell membrane tyrosine kinase receptors (RET, EGF, VEGF, PDGF) into the nucleus. Gene alteration in the RAF/RAS/MEK pathway leads to promotion of cell proliferation, cell growth, and angiogenesis and loss of differentiation, while mutation in the PI3K/AKT/mTOR pathway results in tumor progression. Red arrows show the targets of the therapeutic agents.

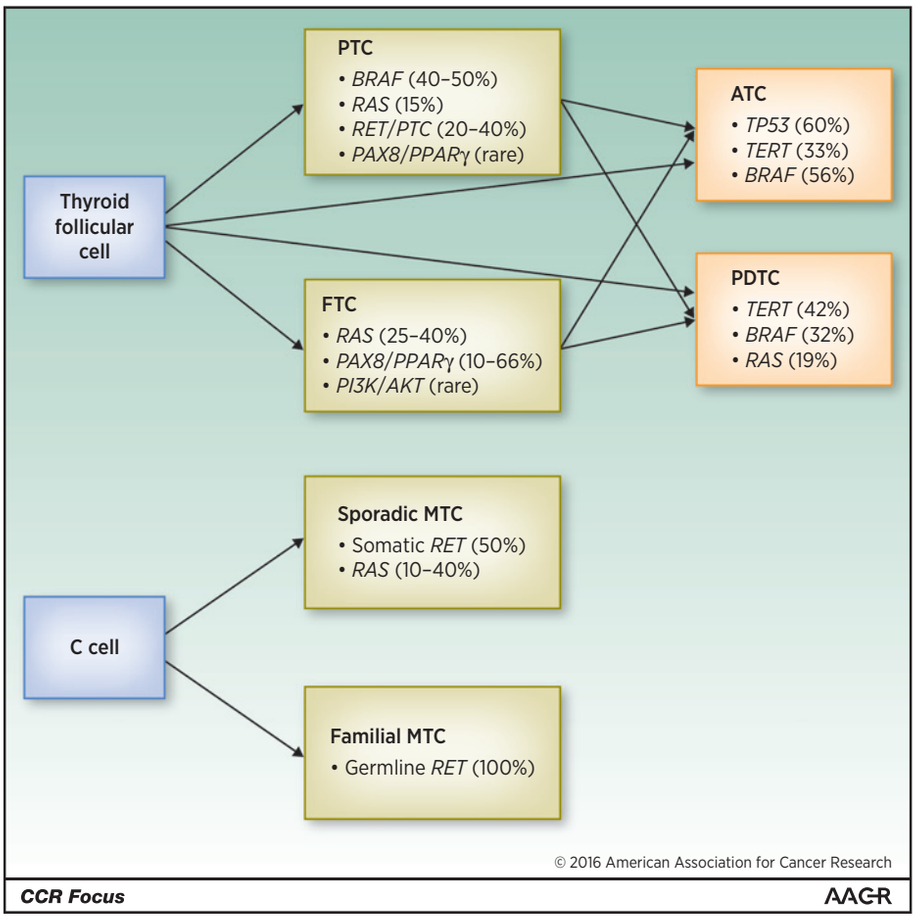

Figure 2.
Main subtypes of thyroid cancer and most prevalent oncogenic driving lesions (in percentages; ref. 110).

alterations that have been described for thyroid cancer and the most recent efforts to find other activated oncogenes, approximately 5% to 10% of PTCs, 50% to 60% of MTCs, and 10% of ATCs are still negative for all known genetic abnormalities (38, 39).

Mutations identified may have diagnostic and prognostic implications, and provide an opportunity to develop therapies that are targeted at these potential molecular drivers. *BRAF* mutations are present in 30% to 67% of PTCs and are associated with locoregional metastases, extrathyroidal extension, and higher AJCC stage at presentation (refs. 40–43; Fig. 2). Both *BRAF* and *TERT* promoter mutations, which in one study were present in 13% of 242 PTCs, were associated with the clinicopathologic features of high-risk thyroid cancer (44). These and other genetic mutations and rearrangements, such as those affecting *RAS*, *RET/PTC*, and *PAX8/PPARϒ*, are now used as molecular markers and included in a multigene mutational panel investigated in FNA or surgically resected specimens. Using this gene panel to analyze thyroid nodules with indeterminate cytology (Bethesda system) showed 91% sensitivity and 92% specificity for cancer detection, and a 97% negative predictive value and a 77% positive predictive value (15, 45). Another approach to molecular diagnosis of intermediate thyroid nodules is the gene expression classifier using extracted RNA and analysis of 167 transcripts (46). The gene expression classifier has a sensitivity of 92% and 52% specificity, negative predictive values of 95%, and negative predictive value of 47%, respectively, for detecting benign nodules (46). Additional studies validating the mutation panels are ongoing (47, 48); long-term outcome data from a strategy of using molecular markers in indeterminate FNA specimens to stratify surgical approach are currently lacking (15).

Once thyroid cancer is highly suspected or diagnosed, a decision must be made regarding the extent of surgery. Risk factors must be taken into consideration, like clinical risk factors associated with aggressive tumor behavior, the patient's age and sex, the initial tumor size and location, the presence of lymph node and/or distant metastases, cytologic and mutational data, and patient preferences. A positive test for *BRAF* mutations means a close to 100% probability of malignancy (49, 50)—this is likely helpful to guide the extent of thyroidectomy.

Surgical Therapy for DTC

The treatment for thyroid cancer is predominantly surgical, and total thyroidectomy with preservation of the recurrent laryngeal nerve and parathyroid glands is generally considered standard. This achieves disease clearance and minimizes the risk of thyroid bed recurrence. A second aim of primary surgery is preparing the patient for adjuvant radioactive iodine (RAI) therapy by removing all thyroid tissue. This allows optimal follow-up using thyroglobulin (TG) as a tumor marker and addresses concerns about multifocal disease within the gland. PTC commonly metastasizes to the central neck, followed by the lateral neck. If this is

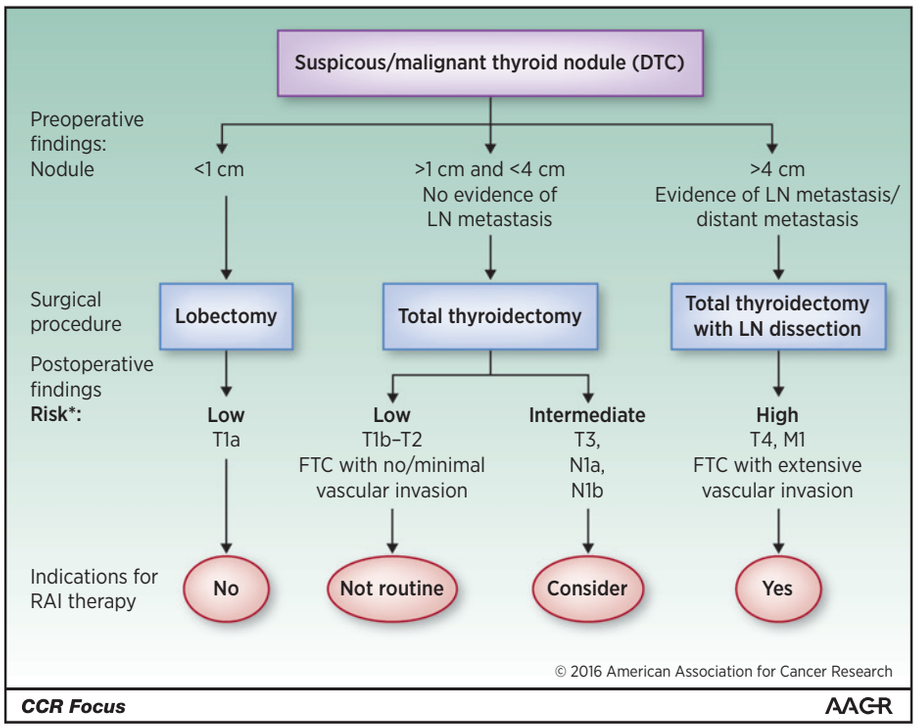

Figure 3.
Surgical and RIA treatment in patients with differentiated thyroid cancer. *, for further details of risk classification, see the American Thyroid Association guidelines (15).

documented in the preoperative work-up, then compartment-oriented lymph node neck dissection is recommended (15).

The decision to use standard aggressive surgical treatment remains controversial due to the excellent outcomes for most patients with DTC, irrespective of the nature of the surgical procedure (refs. 51, 52; Fig. 3). The treatment approaches recommended by the new American Thyroid Association (ATA) guidelines are more conservative (15). High-risk patients are treated aggressively, whereas less-aggressive approaches may be suitable for low-risk patients; indeed, some patients with the lowest risk disease (micropapillary carcinoma distant from the recurrent nerve or trachea) may be candidates for an observational approach (53, 54) or thyroid lobectomy (15). Complication rates associated with lobectomy are roughly half of those reported with total thyroidectomy. By balancing all of the tumor-, clinician-, and patient-related factors, a risk-adapted approach can be used to tailor a treatment plan for each patient to optimize outcomes on a case-by-case basis.

RAI Treatment

Traditionally, RAI treatment has been used in all patients with DTC to ablate residual thyroid tissue and to postoperatively eradicate possible residual cancer, thereby decreasing the long-term risk of recurrent disease (55, 56). It should not be used in patients with ATC, even if they have DTC in addition to ATC in the pathology. It can also be used to identify and treat patients with distant metastatic disease that is sensitive to RAI. Side effects are common with I-131 therapy, including salivary gland dysfunction (>40%), abnormally dry eyes (25%), transient fertility reduction (20%), transient leukopenia, and thrombocytopenia (57). Guidelines now recommend a selective use of RAI, based on a risk-adapted, individualized approach, although RAI is still recommended in patients with aggressive primary lesions or metastatic disease in the neck or beyond. RAI remnant ablation is not recommended (tumor diameter <1 cm) or not routinely recommended (tumor diameter 1–4 cm) after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma in the absence of other adverse features (15).

Follow-up Treatment of DTC

After initial therapy, all patient data must be considered to determine follow-up treatment, including information obtained prior to surgery and the intra- and postoperative findings. These data are essential components for initial risk stratification. In the future, molecular testing results will be incorporated into this process, as, for example, a TERT mutation is an independent predictor of mortality for all differentiated cancers and for papillary carcinomas (58). Older staging systems, such as EORTC, AGES, AMES, MACES, and MSK, based mainly on the extent of tumor and age shortly after initial therapy, provide good risk stratification, but they fail to predict the risk of recurrence (59–62). The ATA guidelines include the results of postoperative US, postablative whole-body scan (WBS) if done, serum TG measurement, and, in cases where available, analysis of BRAF and/or TERT status for initial risk estimation (15). Patients are classified as low, intermediate, or high risk of recurrence, and this is modified as new data are collected during follow-up (15).

The initial follow-up plan for low-risk patients (inconspicuous US of the neck and serum TG <0.2 pg/mL) includes a visit 6 to 12 months after the initial risk assessment, with a target thyroid-stimulating hormone (TSH) level of 0.5 to 1.5 mIU/L for thyroid hormone therapy. Diagnostic RAI scans are seldom needed in these patients because nearly all recurrences can be identified by serum TG and neck US. The primary goal of early follow-up for

low-risk patients is to identify patients that demonstrate an excellent response to therapy (remission) and can quickly be transitioned to a much less-intense follow-up program.

Intermediate-risk patients (TG level >5 ng/mL) are initially followed at 6-month intervals with an US and a target TSH in the 0.1 to 0.5 mIU/L range. A nonstimulated elevated TG level at 6 or more weeks after a completion thyroidectomy alerts the clinician to look for residual thyroid tissue or metastatic disease that remains after surgery (63). Diagnostic RAI scans may be used to characterize the functional status of structural disease identified during follow-up or to localize the source of markedly elevated or rising serum TG levels. Additional imaging studies may be necessary. The goal of follow-up for intermediate-risk patients is to identify the 30% of intermediate-risk patients that rapidly go into remission and can be transitioned to less-intense follow-up and the 70% of patients that do not go into remission and who might benefit from additional observation, imaging, or intervention.

The majority of high-risk patients have persistent disease after initial therapy. Therefore, the dynamics, intensity, and type of imaging used over the course of the first year vary by individual but should occur on average every 3 months. The target TSH level in high-risk patients is usually 0.1 mIU/L. Diagnostic RAI scans are frequently used to follow up these patients, particularly if RAI avid disease was identified previously.

The follow-up management strategy should be designed to optimize follow-up frequency and to determine the extent of additional testing that is needed to identify persistent or recurrent disease in a timely fashion (dynamic risk assessment; 64–67). During follow-up, the response to therapy is classified as an excellent, biochemical incomplete, structural incomplete, or indeterminate response. An excellent response is defined as no biochemical, structural, or functional evidence of disease, with a risk of recurrence of 1% to 2%. Patients with a biochemical incomplete response to therapy have an abnormal serum TG level without structurally identifiable disease. If the serum TG is increasing, then additional imaging is warranted, depending on the TG level and its increase over time; this is often expressed as the TG doubling time (68). Patients with structurally identifiable disease are classified as having a structural incomplete response to therapy with disease-specific prognostic outcomes (65). In such patients, further therapy is necessary and depends on the location of metastases, the rate of progression, the RAI avidity, and the response to previous therapies. Localized treatments can be considered for patients with progressive disease, thereby delaying the need for systemic treatment [e.g., external beam radiation or embolization for bone or liver metastases in patients in whom these are symptomatic or likely to cause morbidity (15)]. Decision making requires that the clinician and the patient carefully weigh the risks and benefits of additional therapy, as the majority of patients will not be disease free, even after additional treatment.

MTC

MTC accounts for less than 5% of thyroid cancer and has some special features: it arises from the C cells of the thyroid, which do not accumulate radioiodine; it secretes calcitonin (Ctn), which is used as a tumor marker; and 25% are part of the autosomal-dominant syndrome, multiple endocrine neoplasia type 2 (MEN2), which is caused by germline-activating mutations in the *RET* proto-oncogene (69). These features allow early recognition of sporadic MTC using Ctn screening in patients with thyroid nodules and preclinical diagnosis of patients with MEN2 by *RET* gene analysis. The ATA guidelines recommend that physicians decide whether the Ctn screening is useful in the management of patients in their clinics (20). The sensitivity of Ctn measurement for the preoperative diagnosis of MTC is higher than that of FNA, with Ctn showing approximately 100% sensitivity and 95% specificity (70–72). Surgery represents the only curative therapeutic strategy. MTC cure is possible in early-stage disease that is detected by Ctn screening before the tumor has metastasized beyond the thyroid and in MEN2 patients by prophylactic thyroidectomy. Sex-specific cut-off values have been proposed to improve the accuracy of basal Ctn levels for mandating total thyroidectomy (20–30 pg/mL for women, 60–79 pg/mL for men; refs. 73, 74). The recommendations for timing prophylactic thyroidectomy in MEN2 patients are based on a model that utilizes genotype–phenotype correlations to stratify mutations into three risk levels—(i) highest (patients with MEN2B and RET M918T mutation, operated in the first year), (ii) high (patients with MEN2A and RET 634 and 883 mutation, operated before the age of 5 years), and (iii) moderate risk (patients with all other mutations, operated on Ctn levels)—that reflect the aggression level of the MTC (20, 75). For patients with moderate-risk mutations, the decision regarding the age at which prophylactic thyroidectomy should be performed is no longer based upon genotype alone but is driven by additional clinical data, especially basal or stimulated serum Ctn levels (75–79). Surgery may be postponed until the patient has an abnormal basal Ctn level.

After surgery, the presence of residual disease, the localization of metastases, and the presence of progressive disease should be assessed to stratify patients with low-risk versus high-risk MTC (20). Somatic *918 RET* mutations are a very strong factor for poor prognosis in MTC. A dynamic risk stratification system that uses a combination of the TNM/AJCC staging system, postoperative nadir of Ctn and CEA, and imaging studies to identify local recurrences or distant metastases allows the stratification of MTC patients into three risk groups (80, 81).

1. Patients with undetectable postoperative Ctn levels who are likely to be disease-free and have an excellent prognosis (10-year survival >95%). This group includes 60% to 90% of patients with a small tumor and no lymph node involvement, but only 20% of those with lymph node metastases. Long-term observation without any further treatment is sufficient. Serum Ctn becomes detectable during follow-up in only 3% of these patients (82).
2. Patients with detectable Ctn levels after initial treatment with no initial evidence of disease in routine imaging (biochemical incomplete response). Elevations in serum Ctn <150 pg/mL following total thyroidectomy are usually associated with locoregional disease and, very rarely, with distant metastases (83, 84). These patients might be candidates for a second surgery with curative intent. Unfortunately, many patients with MTC who have regional lymph node metastases also have systemic disease and are not cured biochemically despite aggressive surgery, including bilateral neck dissection (85, 86). In all other asymptomatic patients, watchful waiting and, primarily, careful examination by neck US is sufficient (87). In most cases with comprehensive follow-up examinations, tumor markers increase slowly; local recurrence or small, slow-growing, or stable distant

Table 1. Tyrosine kinase inhibitors (TKI) used in thyroid cancer

Substance	Drug targets	Cancer	No. of patients, verum vs. placebo	PFS (months), verum vs. placebo	PR (%), verum vs. placebo	Ref.
Phase III clinical trials with approved TKI for advanced thyroid cancer						
Sorafenib	VEGF1,2,3 RET, BRAF, PDGFR	DTC	207 vs. 210	10.8 vs. 5.8	12.2 vs. 0.5	99
Lenvatinib	VEGF1,2,3 RET, PDGFR, FGFR1,2,3,4	DTC	261 vs. 131	18.3 vs. 3.6	63.2 vs. 1.5	100
Vandetanib	VEGFR2, RET, EGFR	MTC	231 vs. 100	30.5 vs. 19.3	45 vs. 13	97
Cabozantinib	VEGFR2, RET, MET	MTC	219 vs. 111	11.2 vs. 4.0	28 vs. 0	98
Phase II clinical trials with TKI and mTOR inhibitors for thyroid cancer						
Axitinib	VEGFR1,2,3	DTC/MTC	52	16.1	35	111
Everolimus	mTOR	MTC	7	8.3	NA	112
Gefitinib	EGFR	DTC	18	3.7	3.7	113
		ATC	5	NA	0	
Imatinib	Bcr-Abl, c-KIT, PDGFR, RET	MTC	15	NA	0	114
		MTC	9	NA	0	115
		ATC	8	NA	25	116
Lenvatinib	VEGFR, c-KIT, RET, PDGFR, FGFR	MTC	59	9		117
Motesanib	VEGFR, PDGFR, c-KIT	DTC	93	10	14	118
		MTC	91	12	2	119
Pazopanib	VEGFR, c-KIT PDGFR, RET, FGRF	DTC	37	11.7	49	120
		ATC	15	NA	0	121
Selumetinib	MEK1,2	DTC	32	8	3	122
Sorafenib	VEGFR, RET, PDGFR, FGFR, c-KIT, BRAF	DTC	31	14	25	123
		MTC	16	17.9	6	124
		ATC	20	1.9	10	125
Sunitinib	VEGFR, c-KIT PDGFR, RET	DTC	29	NA	28	126
Vemurafenib	$BRAF^{V600E}$	PTC $BRAF^{V600E}$ positive	51	NA	38	127

Abbreviations: NA, not available; PFS, progression-free survival; PR, partial response.

metastases without clinical symptoms are detected by imaging in 40% of cases during 10 years of follow-up. If any treatment is necessary, local treatment may be sufficient. Active surveillance is appropriate in most cases.

3. Patients in an advanced stage of disease with distant metastases at diagnosis and high tumor marker levels (structural incomplete response). These patients have a poor prognosis, with only 40% surviving for 10 years (88). Imaging is used to document metastasis sites, tumor volume, and progression rate (89–91). The growth rate of selected metastases can be determined by sequential imaging studies every 3 to 6 months using Response Evaluation Criteria in Solid Tumors (RECIST; ref. 92) and by measuring serum levels of Ctn or CEA over time to determine the tumor marker doubling time, as tumor marker and tumor mass are correlated (93, 94). Evaluating symptomatic disease manifestation is crucial for making decisions about therapy, such as palliative surgery of metastases, external beam radiation of bone metastases, chemoembolization of liver metastases or administration of systemic therapy like tyrosine kinase inhibitors (TKI). The clinician and patient should discuss expectations regarding quality of life, and the risks and benefits of therapy to determine the best personalized treatment plan. The treatment decision must, therefore, balance the progression rate of the tumor and the quality of life without treatment against the efficacy and side effects of therapy. As none of the possible treatments are curative, palliative therapy should aim to improve quality of life by relieving symptoms (best supportive care). The goals are to provide locoregional disease control, to palliate symptoms of hormonal excess such as diarrhea, to palliate symptomatic metastases like pain or bone fracture, and to control life-threatening metastases such as bronchial obstruction or spinal cord compression.

TKI Therapy for Advanced-Stage Thyroid Cancer

Before the advent of targeted therapies, chemotherapy was the only option for treating patients with progressive advanced thyroid cancer, but it had only minor efficiency (95). The oncogene pathway–driven approach to understanding the pathophysiology of thyroid cancer prompted clinical trials to assess the antitumor activity of TKIs that inhibit the RET kinase, VEGFR, and other kinases (Fig. 1). Thus, treatment with TKI is indicated in patients

Table 2. Any grade of common adverse events associated with different TKI

Sorafinib (99)	Lenvatinib (100)	Vandetanib (97)	Cabozantinib (98)
Hand–foot syndrome 75%	Hypertension 68%	Diarrhea 56%	Diarrhea 63%
Diarrhea 69%	Diarrhea 60%	Rash 45%	Hand–foot syndrome 50%
Alopecia 67%	Fatigue 59%	Nausea 33%	Decreased weight 48%
Rash 50%	Decreased appetite 50%	Hypertension 32%	Decreased appetite 46%
Weight loss 47%	Decreased weight 46%	Fatigue 24%	Nausea 43%
Hypertension 41%	Nausea 41%	Headache 26%	Fatigue 41%
Anorexia 32%	Stomatitis 36%	Decreased appetite 21%	Dysgeusia 34%
Oral mucositis 23%	Hand–foot syndrome 32%	Acne 20%	Hypertension 33%

with significant tumor burden and documented tumor progression, or those with disease that is threatening vital structures or causing substantial clinical symptoms. Patients with DTC should have RIA-refractory disease before TKIs are considered. This is important because patients with DTC or MTC often have indolent disease, and localized treatment for local control and palliation should be considered first. In patients with metastatic MTC, progression is documented by RECIST (92) and shortened doubling times (<6 months) of serum Ctn and CEA levels (96). Systemic therapy should not be administered to patients with increasing serum Ctn and CEA levels who do not have documented metastatic disease, to patients with stable low-volume metastatic disease as determined by imaging studies, or patients with serum Ctn and CEA doubling times greater than 2 years. Vandetanib (ZETA trial) and cabozantinib (EXAM trial) are approved for the treatment of MTC (97, 98), and sorafenib (DECISION trial) and lenvatinib (SELECT trial) for progressive radioiodine-refractory PTC and FTC (refs. 99, 100; Table 1). All TKI phase III studies have demonstrated significant improvement in progression-free survival, but not in overall survival. However, in a subgroup analysis, a statistically significant difference in overall survival (44.3 months vs. 18.9 months; HR 0.60; 95% CI, 0.38–0.95) was observed in patients with MTC and somatic *RET M918T* mutations who received cabozantinib compared with placebo (101). In another subgroup, analysis of older patients (>65 years) from the SELECT trial who were treated with lenvatinib had an improved overall survival compared with placebo (102). In patients with ATC and *BRAF V600F* mutation, a study with the selective BRAF inhibitor vemurafenib was done (103). Selumetinib, a MEK1/2 inhibitor was found to reverse refractoriness to RAI in patients with metastatic DTC (104).

Details of clinical trials in thyroid cancer are summarized in Table 1 and can be found elsewhere (105, 106). A limitation of targeted therapy is the development of an escape mechanism. This phenomenon of resistance to treatment is almost always present, independent of the type of TKI used and the type of human tumor treated (107, 108). TKIs have substantial and unique toxicity profiles, and the doses must be reduced or treatment halted in a significant proportion of patients (Table 2). Common adverse effects associated are hand–foot skin reaction, hypertension, diarrhea, rash, fatigue, weight loss, and QTc prolongation (109). Few data are available on their long-term toxicity.

Conclusions

Characterization of the molecular mechanisms and mutations that affect key signaling pathways in thyroid cancer pathogenesis is now being translated into clinical practice, with increasing effects on patient care and more specifically on cancer diagnosis, prognostication, and targeted therapies. *TERT* promoter mutations, RET, and *BRAF* mutations are major molecular biomarkers of prognosis. Mutation analysis of thyroid nodule FNA samples helps determine the initial treatment and affects postoperative risk stratification in patients with thyroid cancer.

Disclosure of Potential Conflicts of Interest

F. Raue is a consultant/advisory board member for AstraZeneca, Eisai, Sanofi Genzyme, and Swedish Orphan Biovitrum. K. Frank-Raue is a consultant/advisory board member for AstraZeneca, Sanofi Genzyme, and Swedish Orphan Biovitrum. No other potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: F. Raue, K. Frank-Raue
Development of methodology: F. Raue, K. Frank-Raue
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F. Raue
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Raue, K. Frank-Raue
Writing, review, and/or revision of the manuscript: F. Raue, K. Frank-Raue
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Raue
Study supervision: F. Raue, K. Frank-Raue

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